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I, JONNE YABSLEY, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2002952331 for a patent by FUJISAWA PHARMACEUTICAL CO., LTD and DAISO CO., LTD as filed on 29 October 2002.

WITNESS my hand this
Seventeenth day of October 2003

J R Yabsley

JONNE YABSLEY
TEAM LEADER EXAMINATION
SUPPORT AND SALES

Regulation 3.2

Fujisawa Pharmaceutical Co., Ltd.
AND
DAISO CO., LTD.

**A U S T R A L I A**

**Patents Act 1990**

**PROVISIONAL SPECIFICATION**

for the invention entitled:

**"Amide Compounds"**

The invention is described in the following statement:

DESCRIPTION

# AMIDE COMPOUNDS

## TECHNICAL FIELD

This invention relates to new amide compounds and salts thereof which inhibit apolipoprotein B (Apo B) secretion and are useful as a medicament.

## BACKGROUND ART

Apo B is the main component of lipoprotein such as VLDL (very low density lipoprotein), IDL (intermediate density lipoprotein) and LDL (low density lipoprotein). Compounds that inhibit Apo B secretion are useful for the treatment of diseases or conditions resulting from elevated circulating levels of Apo B, such as hyperlipemia, hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia, hypertriglyceridemia, atherosclerosis, pancreatitis, non-insulin dependent diabetes mellitus (NIDDM), obesity and coronary heart diseases. Compounds that inhibit Apo B secretion have been described in WO96/40640, WO98/23593, WO98/56790 and WO00/32582. Compounds that inhibit Apo B secretion are also useful in reducing intestinal fat absorption, reducing food intake and treating obesity in combination with a known anti-obesity agent (EP 1 099 438, EP 1 099 439 and EP 1 099 441).

## DISCLOSURE OF INVENTION

This invention relates to new amide compounds.

One object of this invention is to provide new and useful amide compounds and salts thereof that inhibit Apo B secretion.

A further object of this invention is to provide a pharmaceutical composition comprising said amide compound or a pharmaceutically acceptable salt thereof.

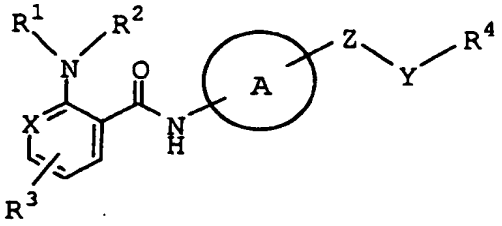
Still further object of this invention is to provide a use of said amide compounds or pharmaceutically acceptable salts thereof as a medicament for prophylactic and therapeutic treatment of diseases or conditions resulting from elevated circulating levels of Apo B, such as hyperlipemia, hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia, hypertriglyceridemia, atherosclerosis, pancreatitis, non-

insulin dependent diabetes mellitus (NIDDM), obesity, coronary heart diseases, myocardial infarction, stroke, restenosis and Syndrome X.

Another object of this invention is to provide a method for inhibiting or decreasing Apo B secretion in a mammal, which comprises administering an Apo B secretion inhibiting or decreasing amount of said amide compound or a pharmaceutically acceptable salt thereof to the mammal.

Still further object of this invention is to provide a method for preventing or treating a disease or condition resulting from elevated circulating levels of Apo B in a mammal, such as hyperlipemia, hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia, hypertriglyceridemia, atherosclerosis, pancreatitis, NIDDM, obesity, coronary heart diseases, myocardial infarction, stroke, restenosis and Syndrome X, which method comprises administering an effective amount of said amide compound or a pharmaceutically acceptable salt thereof to the mammal.

The object amide compounds of the present invention are novel and can be represented by the following general formula (I)



(I)

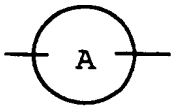
wherein

$R^1$ and $R^2$ are each independently lower alkyl, or $R^1$, $R^2$ and nitrogen atom to which they are attached form an optionally substituted, saturated or partially saturated N-containing heterocyclic group;

$R^3$ is hydrogen, halogen, lower alkyl, lower alkoxy, halo(lower)alkyl or $-NR^5R^6$ (wherein $R^5$ and $R^6$ are each independently lower alkyl, or $R^5$, $R^6$ and nitrogen atom to which they are attached form an optionally substituted, saturated or partially saturated N-containing

heterocyclic group);

$R^4$ is aryl or heteroaryl, each of which is optionally substituted by cyano, amino, lower alkyl or heteroaryl substituted by one or more lower alkyl;




is bivalent residue derived from aryl or heteroaryl;

X is N or $C(R^3)$ (wherein $R^3$ is as defined above);

Y is $-(A^1)_n-(A^2)_m-$

wherein $A^1$ is -O-, -NH-, $-N(R^7)-$, -CO- or -NH-CO-,

wherein $R^7$ is amino protective group,

$A^2$ is lower alkylene, and

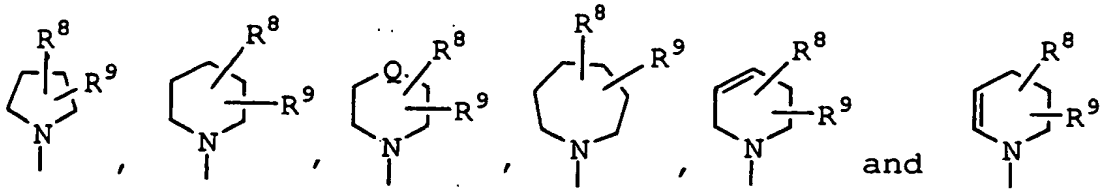
n and m are independently 0 or 1; and

Z is direct bond or bivalent residue derived from piperazine, or a salt thereof.

The preferred embodiments of the amide compound of the present invention represented by the general formula (I) are as follows.

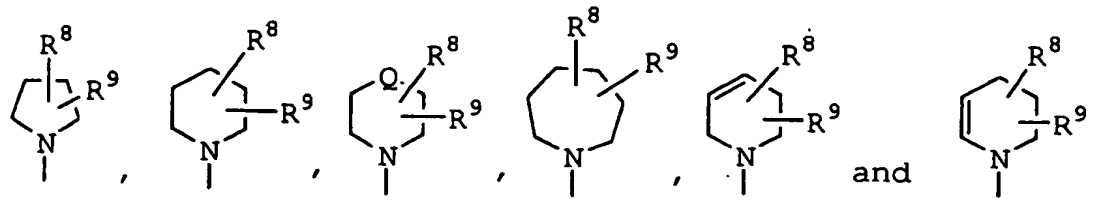
(1) The compound of the formula (I) above wherein

$R^1$ and $R^2$ are each independently lower alkyl, or $R^1$, $R^2$ and nitrogen atom to which they are attached form a saturated or partially saturated N-containing heterocyclic group selected from



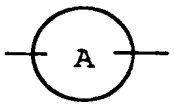

wherein $R^8$ and $R^9$ are each independently hydrogen or lower alkyl, and Q is $-N(R^{10})-$, -O-, -S-, -SO- or $-SO_2-$ wherein $R^{10}$ is hydrogen or lower alkyl;

$R^3$ is hydrogen, halogen, lower alkyl, lower alkoxy, halo(lower)alkyl or $-NR^5R^6$ (wherein $R^5$ and $R^6$ are each independently lower alkyl, or $R^5$, $R^6$ and nitrogen atom to which they are attached form a saturated or partially saturated N-containing heterocyclic group selected from



wherein $R^8$, $R^9$ and Q are as defined above);

$R^4$ is phenyl, pyridinyl, pyrimidinyl or thiazolyl, each of which is optionally substituted with cyano, amino, lower alkyl or pyrrolyl substituted with one or more lower alkyl; and



is phenylene, pyridinediyl or indolinediyl,

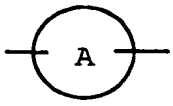
or a salt thereof.

(2) The compound of the formula (I) above wherein

$R^1$ and $R^2$ are each independently lower alkyl;

$R^3$ is hydrogen, halogen, lower alkyl, lower alkoxy or halo(lower)alkyl;

$R^4$ is phenyl, pyridinyl, pyrimidinyl or thiazolyl, each of which is optionally substituted with cyano, amino, lower alkyl or pyrrolyl substituted with one or more lower alkyl; and



is phenylene,

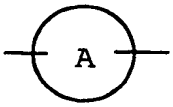
or a salt thereof.

(3) The compound of the formula (I) above wherein

$R^1$ and $R^2$ are each independently lower alkyl;

$R^3$ is hydrogen, halogen, lower alkyl, lower alkoxy or halo(lower)alkyl;

$R^4$ is phenyl, pyridinyl, pyrimidinyl or thiazolyl, each of which is optionally substituted with cyano, amino, lower alkyl or pyrrolyl substituted with one or more lower alkyl; and

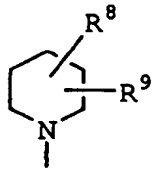



is indolinediyl,

or a salt thereof.

(4) The compound of the formula (I) above wherein

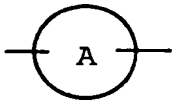
$R^1$, $R^2$ and nitrogen atom to which they are attached form a saturated N-containing heterocyclic group of the formula




wherein $R^8$ and $R^9$ are each independently hydrogen or lower alkyl;

$R^3$ is hydrogen, halogen, lower alkyl, lower alkoxy or halo(lower)alkyl;

$R^4$ is phenyl, pyridinyl, pyrimidinyl or thiazolyl, each of which is optionally substituted with cyano, amino, lower alkyl or pyrrolyl substituted with one or more lower alkyl; and

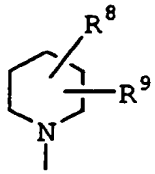



is phenylene,

or a salt thereof.

(5) The compound of the formula (I) above wherein

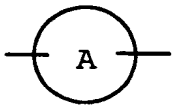
$R^1$, $R^2$ and nitrogen atom to which they are attached form a saturated N-containing heterocyclic group of the formula




wherein $R^8$ and $R^9$ are each independently hydrogen or lower alkyl;

$R^3$ is hydrogen, halogen, lower alkyl, lower alkoxy or halo(lower)alkyl;

$R^4$ is phenyl, pyridinyl, pyrimidinyl or thiazolyl, each of which is optionally substituted with cyano, amino, lower alkyl or pyrrolyl substituted with one or more lower alkyl; and




is indolinediyl,

or a salt thereof.

Suitable salts of the object compound (I) may be pharmaceutically acceptable salts such as conventional non-toxic salts and include, for example, a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g., sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), an ammonium salt; a salt with an organic base, for example, an organic amine salt (e.g., triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.); an inorganic acid addition salt (e.g., hydrochloride, hydrobromide, sulfate, phosphate, etc.); an organic carboxylic or sulfonic acid addition salt (e.g., formate, acetate, trifluoroacetate, maleate, tartrate, citrate, fumarate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.); and a salt with a basic or acidic amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.).

In the above and subsequent descriptions of the present specification, suitable examples and illustration of the various definitions which the present invention intends to include within the scope thereof are explained in detail as follows.

The term "lower" is used to intend a group having 1 to 6, preferably 1 to 4, carbon atom(s), unless otherwise provided.

Suitable "lower alkyl" includes straight or branched

alkyl having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, tert-pentyl and hexyl, in which more preferred one is $C_1$-$C_4$ alkyl.

Suitable "lower alkoxy" includes straight or branched alkoxy having 1 to 6 carbon atom(s), such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, tert-pentyloxy and hexyloxy, in which more preferred one is $C_1$-$C_4$ alkoxy.

Suitable "halogen" and "halogen" moiety in the term "halo(lower)alkyl" may be fluorine, bromine, chlorine and iodine.

Suitable "halo(lower)alkyl" includes straight or branched haloalkyl having 1 to 6 carbon atom(s) such as fluoromethyl, bromomethyl, chloromethyl, difluoromethyl, dibromomethyl, dichloromethyl, trifluoromethyl, trichloromethyl and tribromomethyl, in which more preferred one is halo($C_1$-$C_4$)alkyl, and the particularly preferred one is trifluoromethyl.

Suitable "lower alkylene" includes straight or branched alkylene having 1 to 6 carbon atom(s), such as methylene, ethylene, trimethylene, tetramethylene, propylene, ethylidene and propylidene, in which more preferred one is $C_1$-$C_3$ alkylene, and the particularly preferred ones are methylene and ethylene.

Suitable examples of "amino protective group" include acyl such as lower alkanoyl (e.g., formyl, acetyl, etc.), lower alkoxycarbonyl (e.g., tert-butoxycarbonyl, etc.), mono(or di or tri)phenyl(lower)alkoxycarbonyl (e.g., benzyloxycarbonyl, etc.), and a conventional protective group such as mono(or di or tri)aryl(lower)alkyl, for example, mono(or di or tri)phenyl(lower)alkyl (e.g., benzyl, benzhydryl, trityl, etc.).

Suitable "lower alkanoyl" includes alkanoyl having 1 to 6 carbon atom(s) such as formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl and hexanoyl, in which more preferred one is $C_1$-$C_4$ alkanoyl.

Suitable "lower alkoxycarbonyl" includes alkoxycarbonyl wherein alkoxy moiety has 1 to 6 carbon atom(s) such as

methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, tert-pentyloxycarbonyl and hexyloxycarbonyl, in which more preferred one is alkoxycarbonyl wherein alkoxy moiety has 1 to 4 carbon atom(s).

Suitable "mono(or di or tri)phenyl(lower)alkoxycarbonyl" includes mono(or di or tri)phenylalkoxycarbonyl wherein alkoxy moiety has 1 to 6 carbon atom(s) such as benzyloxycarbonyl and phenethyloxycarbonyl.

Suitable "mono(or di or tri)phenyl(lower)alkyl" includes mono(or di or tri)phenyl($C_1$-$C_6$)alkyl such as benzyl, benzhydryl and trityl.

Suitable "saturated or partially saturated N-containing heterocyclic group" includes a saturated or partially saturated 4 to 8-membered (more preferably 5 to 7-membered) heteromonocyclic group containing 1 or 2 nitrogen atom(s) and optionally containing oxygen atom or sulfur atom, such as pyrrolidinyl, peperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, hexahydroazepinyl and tetrahydropyridinyl.

"Saturated or partially saturated N-containing heterocyclic group" is optionally substituted by suitable substituent(s) such as lower alkyl and oxo.

Suitable "aryl" includes $C_6$-$C_{12}$ aryl. "Aryl" includes fused carbocyclic group wherein benzene ring is fused with a saturated or unsaturated carbon ring.

Suitable examples of "aryl" include phenyl, naphthyl, indenyl and indanyl, in which more preferred one is phenyl.

Suitable "heteroaryl" includes 5 to 10-membered aromatic heteromonocyclic or fused heterocyclic group containing 1 to 4 heteroatom(s) selected from sulfur atom, oxygen atom and nitrogen atom. "Heteroaryl" includes fused heterocyclic group wherein benzene ring is fused with a saturated or unsaturated heterocyclic ring.

Suitable examples of "heteroaryl" include pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxazolyl, isoxazolyl, furyl, thienyl, indolyl,

isoindolyl, indolizinyl, indazolyl, benzimidazolyl, benzotriazolyl, quinolyl, isoquinolyl, phthalazinyl, quinoxalinyl, quinazolinyl, cinnolinyl, benzofuranyl, benzothienyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, indolinyl, isoindolinyl, tetrahydroquinolinyl and tetrahydroisoquinolinyl.

Suitable "bivalent residue derived from aryl" includes $C_6$-$C_{12}$ arylene. "Bivalent residue derived from aryl" include bivalent fused carbocyclic group wherein benzene ring is fused with a saturated or unsaturated carbon ring.

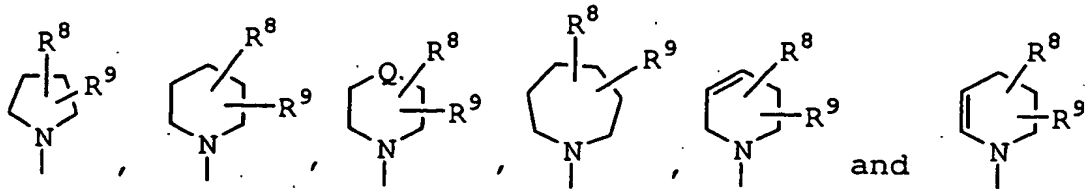
Suitable examples of "bivalent residue derived from aryl" include phenylene, naphthylene, indenediyl and indandiyl, in which more preferred one is phenylene.

Suitable "bivalent residue derived from heteroaryl" includes bivalent 5 to 10-membered aromatic heteromonocyclic or fused heterocyclic group containing 1 to 4 heteroatom(s) selected from sulfur atom, oxygen atom and nitrogen atom. "Bivalent residue derived from heteroaryl" includes bivalent fused heterocyclic group wherein benzene ring is fused with a saturated or unsaturated heterocyclic ring.

Suitable examples of "bivalent residue derived from heteroaryl" include pyridinediyl, pyrimidinediyl, pyrazinediyl, pyridazinediyl, pyrroledlyl, imidazoledlyl, pyrazoledlyl, triazoledlyl, tetrazoledlyl, thiazoledlyl, isothiazoledlyl, thiadiazoledlyl, oxazoledlyl, isoxazoledlyl, furandiyl, thiophenediyl, indoledlyl, isoindoledlyl, indolizinediyl, indazoledlyl, benzimidazoledlyl, benzotriazoledlyl, quinolinediyl, isoquinolinediyl, phthalazinediyl, quinoxalinediyl, quinazolinediyl, cinnolinediyl, benzofurandiyl, benzothiophenediyl, benzoxazoledlyl, benzothiazoledlyl, benzimidazoledlyl, indolinediyl, isoindolinediyl, tetrahydroquinolinediyl and tetrahydroisoquinolinediyl.

Suitable examples of "carboxy protective group" include lower alkyl (e.g., methyl, ethyl, tert-butyl, etc.), mono(or di or tri)phenyl(lower)alkyl optionally substituted by nitro (e.g., benzyl, 4-nitrobenzyl, benzhydryl, trityl, etc.) and lower alkylcarbonyloxy(lower)alkyl (e.g., pivaloyloxymethyl).

Preferable examples of "optionally substituted, saturated or partially saturated N-containing heterocyclic group" include groups of the following formulas:



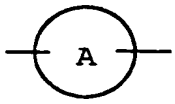
wherein $R^8$ and $R^9$ are each independently hydrogen or lower alkyl, and Q is $-N(R^{10})-$, $-O-$, $-S-$, $-SO-$ or $-SO_2-$ wherein $R^{10}$ is hydrogen or lower alkyl.

Preferable example of "aryl" at $R^4$ is phenyl.

Preferable examples of "heteroaryl" at $R^4$ include 5 or 6-membered aromatic heteromonocyclic group containing 1 to 4 nitrogen atom(s) such as pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl and tetrazolyl, and more preferably pyridinyl.

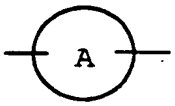
Preferable examples of "heteroaryl substituted by one or more lower alkyl" include pyrrolyl substituted by one or more lower alkyl, and more preferably 2,5-dimethyl-1H-pyrrol-1-yl.

Preferable example of "bivalent residue derived from aryl" at



is phenylene.

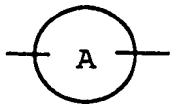
Preferable examples of "bivalent residue derived from heteroaryl" at



include bivalent 5 or 6-membered aromatic heteromonocyclic group containing 1 to 4 nitrogen atom(s) such as pyridinediyl, pyrimidinediyl, pyrazinediyl, pyridazinediyl, pyrroldiyl, imidazoldiyl, pyrazoldiyl, triazoldiyl and tetrazoldiyl; and bivalent 8 to 10-membered fused heterocyclic group containing 1 to 4 nitrogen atom(s) wherein benzene ring is

fused with a saturated or unsaturated heterocyclic ring such as indolinediyl, isoindolinediyl, tetrahydroquinolinediyl and tetrahydroisoquinolinediyl.

More preferably, "bivalent residue derived from heteroaryl" at



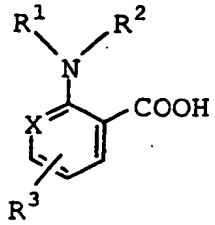
is pyridinediyl or indolinediyl.

Preferable example of "bivalent residue derived from piperazine" at Z is 1,4-piperazinediyl.

Preferable examples of a group represented by Y include $-NH-CO-CH_2-$, $-N(R^7)-(CH_2)_2-$, $-O-CH_2-$, $-CH_2-$ and $-CO-CH_2-$.

The object compound (I) of the present invention can be prepared by the following processes.

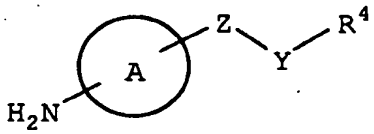
Process (1)



(II)

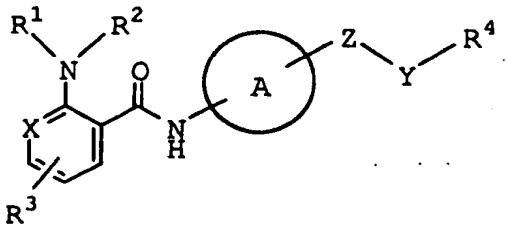
or its reactive derivative at the carboxy group, or a salt thereof

+



(III)

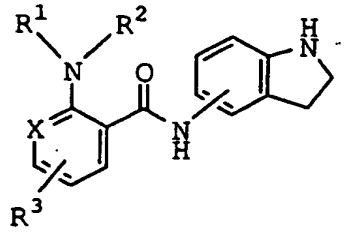
or its reactive derivative at the amino group, or a salt thereof



(I)

or a salt thereof

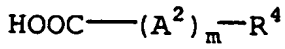
Process (2)



(IV)

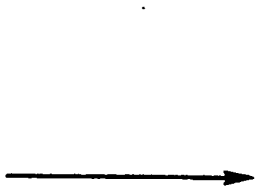
or its reactive derivative at the amino group, or a salt thereof

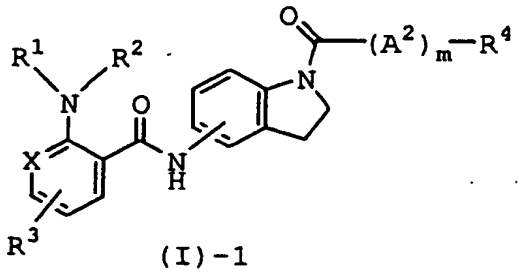
+



(V)

or its reactive derivative at the carboxy group, or a salt thereof

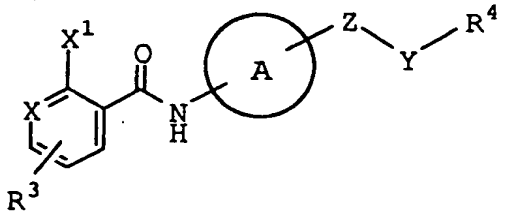




(I)-1

or a salt thereof

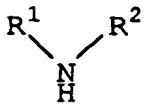
Process (3)



(VI)

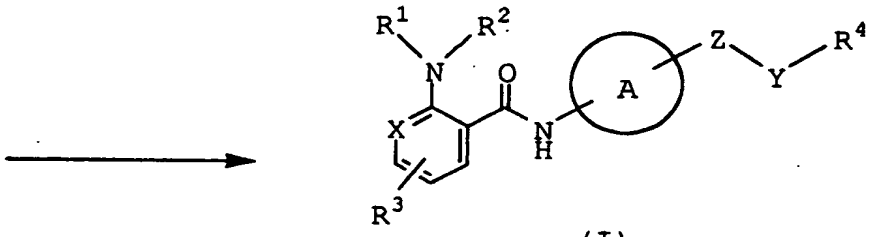
or a salt thereof

+



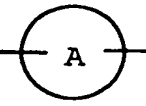
(VII)

or a salt thereof



(I)

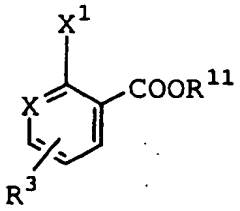
or a salt thereof

wherein $R^1$, $R^2$, $R^3$, $R^4$,  , X, Y, Z, $A^2$ and m are as defined above, and

$X^1$ is leaving group such as halogen (e.g., chlorine, bromine or fluorine) and trifluoromethanesulfonyloxy.

The starting compounds can be prepared by the following processes or by the method of Preparation mentioned below or by a process known in the art for preparing their structurally analogous compounds.

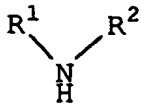
Process (A)



(VIII)

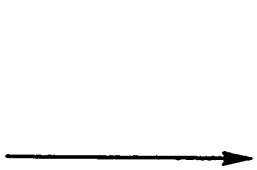
or a salt thereof

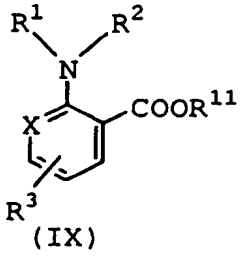
+



(VII)

or a salt thereof

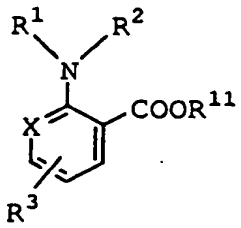




(IX)

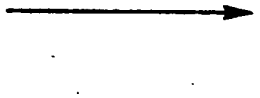
or a salt thereof

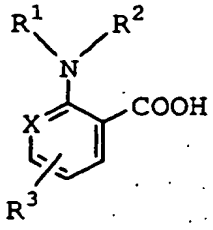
Process (B)



(IX)

or a salt thereof

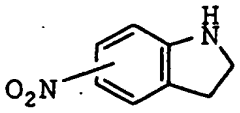




(II)

or a salt thereof

Process (C)



(X)

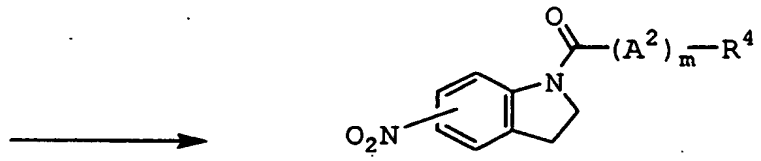
or its reactive derivative at the amino group, or a salt thereof

+

$HOOC-(A^2)_m-R^4$

(V)

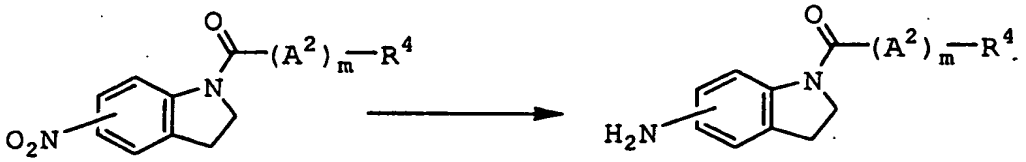
or its reactive derivative at the carboxy group, or a salt thereof



(XI)

or a salt thereof

Process (D)



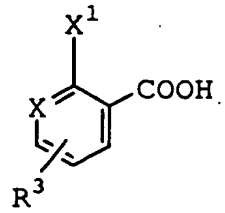
(XI)

or a salt thereof

(III)-1

or a salt thereof

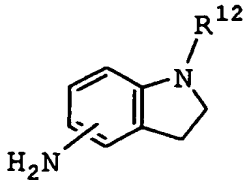
Process (E)



(XII)

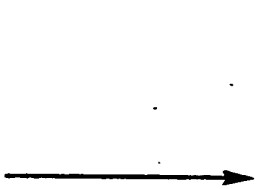
or its reactive derivative at the carboxy group, or a salt thereof

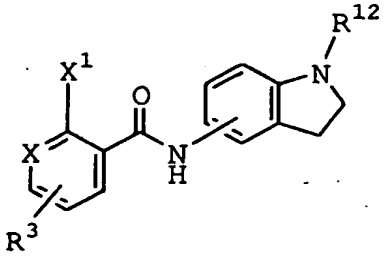
+



(XIII)

or its reactive derivative at the amino group, or a salt thereof

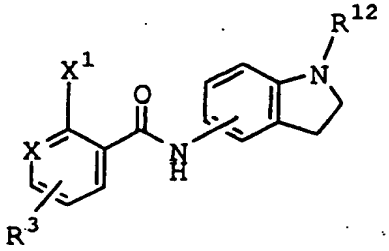




(XIV)

or a salt thereof

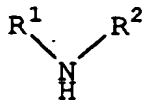
Process (F)



(XIV)

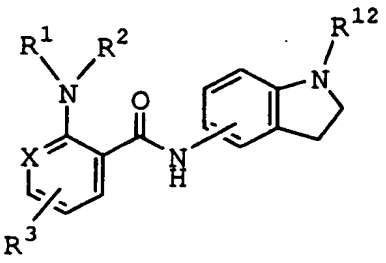
or a salt thereof

+



(VII)

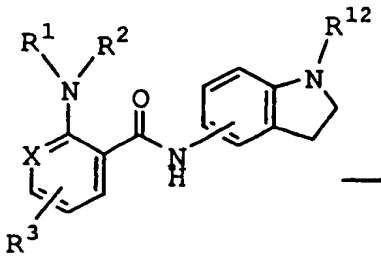
or a salt thereof



(XV)

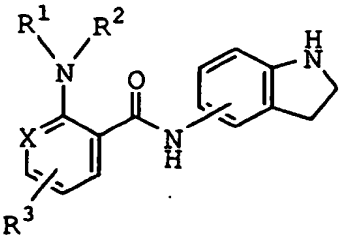
or a salt thereof

Process (G)



(XV)

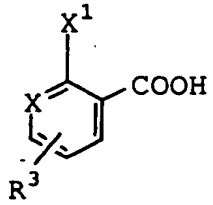
or a salt thereof



(IV)

or a salt thereof

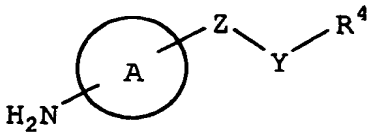
Process (H)



(XII)

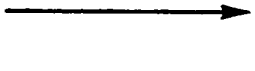
or its reactive derivative at the carboxy group, or a salt thereof

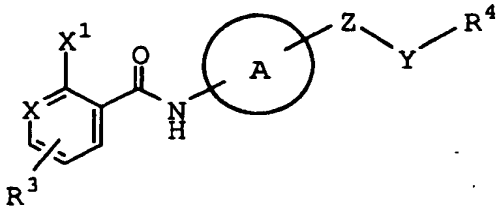
+



(III)

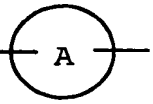
or its reactive derivetive at the amino group, or a salt thereof





(VI)

or a salt thereof

wherein $R^1$, $R^2$, $R^3$, $R^4$,  , X, Y, Z, $A^2$, m and $X^1$ are as defined above,

$R^{11}$ is carboxy protective group, and

$R^{12}$ is amino protective group.

The processes for preparing the object and starting

compounds are explained in detail in the following.

Process (1)

The compound (I) or a salt thereof can be prepared by reacting the compound (II) or its reactive derivative at the carboxy group, or a salt thereof with the compound (III) or its reactive derivative at the amino group, or a salt thereof.

Suitable reactive derivative of the compound (III) includes Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (III) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (III) with a silyl compound such as N,O-bis(trimethylsilyl)acetamide, N-trimethylsilylacetamide or the like; a derivative formed by the reaction of the compound (III) with phosphorus trichloride or phosgene.

Suitable reactive derivative of the compound (II) includes an acid halide, an acid anhydride and an activated ester. The suitable example may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid (e.g., dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.), dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, alkanesulfonic acid (e.g., methanesulfonic acid, ethanesulfonic acid, etc.), sulfuric acid, alkylcarbonic acid, aliphatic carboxylic acid (e.g., pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.); aromatic carboxylic acid (e.g., benzoic acid, etc.); a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; an activated ester (e.g., cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2N^+=CH-$] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridinyl ester,

piperidyl ester, 8-quinolyl thioester, etc.); or an ester with an N-hydroxy compound (e.g., N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxybenzotriazole, N-hydroxyphthalimide, 1-hydroxy-6-chloro-1H-benzotriazole, etc.). These reactive derivatives can optionally be selected from them according to the kind of the compound (II) to be used.

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene dichloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvents which do not adversely affect the reaction, or a mixture thereof.

When the compound (II) is used in free acid form or its salt form in the reaction, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N-carbonyl-bis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; thionyl chloride; oxalyl chloride; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, phosphorus oxychloride, etc.; or the like.

The reaction may also be carried out in the presence of an organic or inorganic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the

reaction is usually carried out under cooling to heating.

Process (2)

The compound (I)-1 or a salt thereof can be prepared by reacting the compound (IV) or its reactive derivative at the amino group, or a salt thereof with the compound (V) or its reactive derivative at the carboxy group, or a salt thereof.

This reaction can be carried out in the same manner as in the aforementioned Process (1), and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of Process (1).

Process (3)

The compound (I) or a salt thereof can be prepared by reacting the compound (VI) or a salt thereof with the compound (VII) or a salt thereof.

The reaction is usually carried out in a conventional solvent such as tetrahydrofuran, dioxane, toluene, methylene chloride, ethylene dichloride, chloroform, N,N-dimethylformamide, N,N-dimethylacetamide or any other organic solvents which do not adversely affect the reaction, or a mixture thereof.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

Process (A)

The compound (IX) or a salt thereof can be prepared by reacting the compound (VIII) or a salt thereof with the compound (VII) or a salt thereof.

The reaction is usually carried out in a conventional solvent such as tetrahydrofuran, dioxane, toluene, methylene chloride, ethylene dichloride, chloroform, N,N-dimethylformamide, N,N-dimethylacetamide or any other organic solvents which do not adversely affect the reaction, or a mixture thereof.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

Process (B)

The compound (II) or a salt thereof can be prepared by subjecting the compound (IX) or a salt thereof to elimination reaction of the carboxy protective group.

Suitable method of this elimination reaction includes conventional one such as hydrolysis, reduction and the like.

(i) For hydrolysis:

The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid.

Suitable base includes an inorganic base and an organic base such as an alkali metal [e.g., sodium, potassium, etc.], an alkaline earth metal [e.g., magnesium, calcium, etc.], the hydroxide or carbonate or hydrogencarbonate thereof, trialkylamine [e.g., trimethylamine, triethylamine, etc.], picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, or the like.

Suitable acid includes an organic acid [e.g., formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.], and an inorganic acid [e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, etc.].

The elimination using Lewis acid such as trihaloacetic acid [e.g., trichloroacetic acid, trifluoroacetic acid, etc.], or the like is preferably carried out in the presence of cation trapping agents [e.g., anisole, phenol, etc.]. This reaction is usually carried out without solvent.

The reaction may be carried out in a conventional solvent such as water, alcohol (e.g., methanol, ethanol, isopropyl alcohol, etc.), tetrahydrofuran, dioxane, toluene, methylene chloride, ethylene dichloride, chloroform, N,N-dimethylformamide, N,N-dimethylacetamide or any other organic solvents which do not adversely affect the reaction, or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

(ii) For reduction:

Reduction is carried out in a conventional manner, including chemical reduction and catalytic reduction.

Suitable reducing reagent to be used in chemical reduction are hydrides (e.g., hydrogen iodide, hydrogen sulfide, lithium aluminum hydride, sodium borohydride, sodium cyanoborohydride, etc.), or a combination of a metal (e.g., tin, zinc, iron, etc.) or metallic compound (e.g., chromium chloride, chromium acetate, etc.) and an organic acid or inorganic acid (e.g., formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.).

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts (e.g., platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.), palladium catalysts (e.g., spongy palladium, palladium black, palladium oxide, palladium on carbon, palladium hydroxide on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.), nickel catalysts (e.g., reduced nickel, nickel oxide, Raney nickel, etc.), cobalt catalysts (e.g., reduced cobalt, Raney cobalt, etc.), iron catalysts (e.g., reduced iron, Raney iron, Ullman iron, etc.), and the like.

The reduction is usually carried out in a conventional solvent such as water, alcohol (e.g., methanol, ethanol, isopropyl alcohol, etc.), tetrahydrofuran, dioxane, toluene, methylene chloride, ethylene dichloride, chloroform, N,N-dimethylformamide, N,N-dimethylacetamide or any other organic solvents which do not adversely affect the reaction, or a mixture thereof.

Additionally, in case that the above-mentioned acids to be used in chemical reduction are in a liquid state, they can also be used as a solvent.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to warming.

Process (C)

The compound (XI) or a salt thereof can be prepared by reacting the compound (X) or its reactive derivative at the amino group, or a salt thereof with the compound (V) or its

reactive derivative at the carboxy group, or a salt thereof.

This reaction can be carried out in the same manner as in the aforementioned Process (1), and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of Process (1).

Process (D)

The compound (III)-1 can be prepared by subjecting the compound (XI) to reduction.

Suitable method of the reduction is catalytic hydrogenation.

Suitable catalysts to be used in the catalytic hydrogenation are conventional ones such as platinum catalysts (e.g., platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.), palladium catalysts (e.g., spongy palladium, palladium black, palladium oxide, palladium on carbon, palladium hydroxide on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.), and the like.

The hydrogenation is usually carried out in a conventional solvent such as water, alcohol (e.g., methanol, ethanol, isopropyl alcohol, etc.), tetrahydrofuran, dioxane, toluene, methylene chloride, ethylene dichloride, chloroform, N,N-dimethylformamide, N,N-dimethylacetamide or any other organic solvents which do not adversely affect the reaction, or a mixture thereof.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

Process (E)

The compound (XIV) or a salt thereof can be prepared by reacting the compound (XII) or its reactive derivative at the carboxy group, or a salt thereof with the compound (XIII) or its reactive derivative at the amino group, or a salt thereof.

This reaction can be carried out in the same manner as in the aforementioned Process (1), and therefore the reagents to be used and the reaction conditions (e.g., solvent,

reaction temperature, etc.) can be referred to those of Process (1).

Process (F)

The compound (XV) or a salt thereof can be prepared by reacting the compound (XIV) or a salt thereof with the compound (VII) or a salt thereof.

This reaction can be carried out in the same manner as in the aforementioned Process (A), and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of Process (A).

Process (G)

The compound (IV) or a salt thereof can be prepared by subjecting the compound (XV) or a salt thereof to elimination reaction of the amino protective group.

This reaction can be carried out in the same manner as in the aforementioned Process (B), and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of Process (B).

Process (H)

The compound (VI) or a salt thereof can be prepared by reacting the compound (XII) or its reactive derivative at the carboxy group, or a salt thereof with the compound (III) or its reactive derivative at the amino group, or a salt thereof.

This reaction can be carried out in the same manner as in the aforementioned Process (1), and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of Process (1).

Suitable salts of the starting compounds and their reactive derivatives in Processes (1) to (3) and (A) to (H) can be referred to the ones as exemplified for the compound (I).

The compounds obtained by the above processes can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography, reprecipitation, or the like.

It is to be noted that the compound (I) and the other compounds may include one or more stereoisomer(s) such as optical isomer(s) and geometrical isomer(s) due to asymmetric carbon atom(s) and double bond(s), and all of such isomers and mixtures thereof are included within the scope of this invention.

The object compounds (I) and pharmaceutically acceptable salts thereof include solvates [e.g., enclosure compounds (e.g., hydrate, etc.)].

The object compounds (I) and pharmaceutically acceptable salts thereof possess a strong inhibitory activity on the secretion of Apo B.

Accordingly, the object compounds (I) and pharmaceutically acceptable salts thereof are useful as an Apo B secretion inhibitor.

The object compounds (I) and pharmaceutically acceptable salts thereof are useful as a medicament for the prophylaxis or treatment of diseases or conditions resulting from elevated circulating levels of Apo B such as hyperlipemia, hyperlipidemia, hyperlipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, atherosclerosis, pancreatitis, non-insulin dependent diabetes mellitus (NIDDM), obesity, coronary heart diseases, myocardial infarction, stroke, restenosis and Syndrome X.

The present invention therefore provides a method for inhibiting or decreasing Apo B secretion in a mammal, in particular in human, which comprises administering an Apo B secretion inhibiting or decreasing amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof to the mammal.

The present invention also provides a method for preventing or treating diseases or conditions resulting from elevated circulating levels of Apo B in a mammal, in particular in human, which comprises administering an

effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof to the mammal.

The object compounds (I) and pharmaceutical acceptable salts thereof are also useful in reducing intestinal fat absorption and reducing food intake for the prophylaxis or treatment of obesity. Furthermore, the object compounds (I) and pharmaceutical acceptable salts thereof possess an inhibitory activity on the lipid transfer of microsomal triglyceride transfer protein (MTP).

In order to illustrate the usefulness of the object compound (I), the pharmacological test result of the compound (I) is shown in the following.

Test Compounds:

2-(dimethylamino)-4-methyl-N-(4-{[2-(2-pyridinyl)ethyl]amino}phenyl)benzamide (Example 42)

2-(4-methyl-1-piperidinyl)-N-(4-{[2-(2-pyridinyl)ethyl]amino}phenyl)nicotinamide (Example 54)

Test 1: Measurement of inhibition of Apo B secretion

HepG2 cells were seeded in Eagles medium containing 10% fetal calf serum (FCS) at a density of 30000 cells/well in 96-well plates and allowed to grow for 3 days before treatment. At this time, the medium was replaced with fresh medium containing 0.1% dimethyl sulfoxide (DMSO) and the indicated concentrations of a test compound. After 15-hour incubation, the amount of Apo B and Apo AI accumulated in the media was determined by ELISA.

The assay was carried out at ambient temperature. A flat bottomed micro ELISA plate (manufactured by Nunc) was coated with an anti Apo B monoclonal antibody solution (5 mg/ml in 0.05% carbonate buffer, pH 9.6) by adding the antibody solution at a volume of 100 µl per well. After 1-hour incubation on a plate mixer, the unbound materials were removed by washing the well 3 times with a washing buffer (phosphate buffered saline, pH 7.2 containing 0.1% bovine serum albumin and 0.05% Tween-20). Then 20 µl of a solution of the test compound (dissolved in the culture medium) and 100

µl of a solution of peroxidase coupled anti Apo B antibody were added. After 1-hour incubation on a plate mixer, washing was performed 3 times to remove the unbound materials. A freshly prepared substrate solution (2.5 mg/ml ortho-phenylene diamine and 0.018% $H_2O_2$ in 0.11 M $Na_2HPO_4$ - 0.044 M sodium citrate buffer, pH 5.4) at a volume of 200 µl was then added to each well. After 20-minute incubation, the enzyme reaction was terminated by adding 50 µl of 0.5 M sulfuric acid. Absorbance of each well was determined at 490 nm using a microplate reader. Apo B concentration was calculated from a standard curve generated from purified Apo B standard that was run in parallel in the same plate. Inhibition of Apo B secretion by the test compound is calculated taking 0.1% DMSO treated cells as controls.

Measurement of Apo AI was performed similar to that of Apo B, except for diluting the sample 11-fold with a dilution buffer (phosphate buffered saline, pH 7.2 containing 0.5% bovine serum albumin and 0.05% Tween-20).

Apo B secretion inhibitors are identified as compounds that decrease Apo B secretion without affecting the secretion of Apo AI.

Test results:

Table 1

| Test compound (Example No.) | Inhibition of Apo B secretion at $10^{-8}$ M (%) |
|---|---|
| 42 | 85.8 |
| 54 | 86.3 |

Test 2: Lipid lowering effect on ddY-mice

Male ddY-mice were housed in temperature- and humidity-controlled rooms and fed with laboratory chow. The animals were randomized according to their body weight and food was deprived about 16 hours before experiment. Baseline blood sample was collected from the retro orbital venous plexus then the animals were orally dosed with drugs in olive oil (10 ml/kg). For control group, 10 ml/kg of olive oil was loaded orally. Blood samples were drawn at 2 hours after drug administration for the measurement of triglyceride (TG)

elevation. Plasma TG was determined by conventional enzyme method (The triglyceride E-test Wako).

Lipid lowering effects were shown in percent of the TG increase in drug treated group, relative to the TG increase in control group.

Lipid lowering effect (%) = (TG increase in drug treated group/TG increase in control group) x 100

Table 2

| Test compound (Example No.) | Dose (mg/kg) | Lipid lowering effect (%) |
|---|---|---|
| 42 | 0.32 | 33 |
| 54 | 0.32 | 28 |

For therapeutic administration, the object compound (I) of the present invention and pharmaceutically acceptable salts thereof are used in the form of a conventional pharmaceutical preparation in admixture with a conventional pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient which is suitable for oral, parenteral or external administration. The pharmaceutical preparation may be compounded in a solid form such as granule, capsule, tablet, dragee, suppository or ointment, or in a liquid form such as solution, suspension or emulsion for injection, intravenous drip, ingestion, eye drop, endermism, inhalation, etc. If needed, there may be included in the above preparation auxiliary substance such as stabilizing agent, wetting or emulsifying agent, buffer or any other commonly used additives.

The effective ingredient may usually be administered in a unit dose of 0.01 mg/kg to 100 mg/kg, preferably 0.1 mg/kg to 10 mg/kg, 1 to 4 times a day. However, the above dosage may be increased or decreased according to age, body weight and conditions of the patient or administering method.

Suitable mammal to which the object compounds (I) and pharmaceutical acceptable salts thereof or above preparations are applied, includes a human being, a companion animal such as a dog and a cat, livestock such as a cow and a pig, and the

like.

The object compounds (I) and pharmaceutical acceptable salts thereof may, if desired, be administered with one or more therapeutic agents and formulated for administration by any convenient route in a conventional manner. Appropriate doses will be readily appreciated by those skilled in the art. For example, the object compounds (I) and pharmaceutical acceptable salts thereof may be administered in combination with an HMG CoA reductase inhibitor. The object compounds (I) and pharmaceutical acceptable salts thereof may be also administered in combination with a known anti-obesity agent, for example, $\beta_3$-adrenergic receptor agonist, a cholecystokinin-A agonist, a monoamine reuptake inhibitor, a sympathomimetic agent, a serotoninergic agent, a dopamine agonist, a melanocyte-stimulating hormone receptor agonist or mimetic, a melanocyte-stimulating hormone receptor analog, a cannabinoid receptor antagonist, a melanin concentrating hormone antagonist, leptin, a leptin analog, a leptin receptor agonist, a galanin antagonist, a lipase inhibitor, a bombesin agonist, a Neuropeptide-Y antagonist, a thyromimetic agent, dehydroepiandrosterone or an analog thereof, a glucocorticoid receptor agonist or antagonist, an orexin receptor antagonist, a urocortin binding protein antagonist, a glucagon-like peptide-1 receptor agonist, a ciliary neurotrophic factor, a human agouti-related protein antagonist, and the like, for the prophylaxis or treatment of obesity.

The following Preparations and Examples are given for the purpose of illustrating the present invention in detail.

Preparation 1

To a suspension of 5-nitroindoline (3.28 g), 2-pyridylacetic acid hydrochloride (3.82 g), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (4.22 g) and 1-hydroxybenzotriazole hydrate (3.37 g) in dichloromethane (100 ml) was added dropwise triethylamine (4.45 g) at ambient temperature and the resultant solution was stirred at ambient temperature for 18 hours. The mixture was poured into water and the separated organic layer was washed with water and brine, dried over magnesium sulfate and

evaporated in vacuo. The residue was purified by column chromatography on silica gel eluting with ethyl acetate to give 5-nitro-1-(2-pyridinylacetyl)indoline (3.58 g) as a yellow solid.

$^1$H-NMR (DMSO-$d_6$):δ 3.26(2H, t, J=8.5 Hz), 4.10(2H, s), 4.33(2H, t, J=8.5 Hz), 7.25-7.35(1H, m), 7.38(1H, d, J=7.8 Hz), 7.75-7.9(1H, m), 8.1-8.2(3H, m), 8.50-8.55(1H, m)

APCI-MS(m/z): 284$(M+H)^+$

Preparation 2

To a solution of 5-nitro-1-(2-pyridinylacetyl)indoline (3.54 g) in methanol (50 ml) and tetrahydrofuran (50 ml) was added 10% palladium on carbon (50% wet, 3.5 g) and the mixture was hydrogenated under hydrogen at atmospheric pressure for 5 hours. After removing the palladium on carbon by filtration, the filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica gel eluting with ethyl acetate:methanol (10:1 v/v) to give 1-(2-pyridinylacetyl)-5-indolinamine (2.16 g) as pale brown crystals.

$^1$H-NMR (DMSO-$d_6$):δ 3.01(2H, t, J=8.4 Hz), 3.92(2H, s), 4.11(2H, t, J=8.4 Hz), 4.84(2H, br s), 6.32(1H, d, J=8.4 Hz), 6.45(1H, s), 7.1-7.2(1H, m), 7.33(1H, d, J=7.8 Hz), 7.7-7.85(2H, m), 8.48(1H, d, J=4.0 Hz)

APCI-MS(m/z): 254$(M+H)^+$

Example 1

1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide (0.19 g) was added to a solution of 1-(2-pyridinylacetyl)-5-indolinamine (0.25 g), 2-(1-pyrrolidinyl)benzoic acid (0.23 g), 1-hydroxybenzotriazole hydrate (0.16 g) and 4-dimethylaminopyridine (6 mg) in N,N-dimethylformamide (5 ml) under ice-cooling and the mixture was stirred at ambient temperature for 18 hours. The reaction mixture was poured into a mixture of ethyl acetate and water. The separated organic layer was washed with water, dried over magnesium sulfate and evaporated in vacuo. The residue was triturated with ethyl acetate to give N-[1-(2-pyridinylacetyl)-2,3-dihydro-1H-indol-5-yl]-2-(1-pyrrolidinyl)benzamide (0.27 g).

$^1$H-NMR (DMSO-$d_6$):δ 1.75-1.95(4H, m), 3.08-3.29(4H, m), 3.16(2H,

t, J=8.4 Hz), 4.00(2H, s), 4.21(2H, t, J=8.4 Hz), 6.65-6.82(2H, m), 7.21-7.47(5H, m), 7.69(1H, s), 7.76(1H, dt, J=1.8 Hz,7.6 Hz), 7.96(1H, d, J=8.7 Hz), 8.50(1H, dd, J=0.9 Hz,4.2 Hz), 10.27(1H, s)

(-)ESI-MS: 425$(M-H)^-$

Example 2

2-(1-Piperidinyl)-N-[1-(2-pyridinylacetyl)-2,3-dihydro-1H-indol-5-yl]benzamide

The title compound was obtained according to a similar manner to that of Example 1 from 1-(2-pyridinylacetyl)-5-indolinamine and 2-(1-piperidinyl)benzoic acid.

$^1$H-NMR (DMSO-$d_6$):δ 1.45-1.76(6H, m), 2.87-3.01(4H, m), 3.19(2H, t, J=8.4 Hz), 4.01(2H, s), 4.23(2H, t, J=8.4 Hz), 7.16-7.57(6H, m), 7.72-7.90(3H, m), 8.02(1H, d, J=8.6 Hz), 8.48-8.55(1H, m), 11.68(1H, s)

(+)APCI-MS: 441$(M+H)^+$

Example 3

2-(3,6-Dihydro-1(2H)-pyridinyl)-N-[1-(2-pyridinylacetyl)-2,3-dihydro-1H-indol-5-yl]benzamide

The title compound was obtained according to a similar manner to that of Example 1 from 1-(2-pyridinylacetyl)-5-indolinamine and 2-(3,6-dihydro-1(2H)-pyridinyl)benzoic acid.

$^1$H-NMR (DMSO-$d_6$):δ 2.21-2.37(2H, m), 3.07-3.27(4H, m), 3.42-3.54(2H, m), 4.00(2H, s), 4.22(2H, t, J=8.4 Hz), 5.77-5.97(2H, m), 7.18-7.44(5H, m), 7.46-7.60(1H, m), 7.67-7.82(2H, m), 7.89(1H, dd, J=1.4 Hz,7.6 Hz), 7.98(1H, d, J=8.6 Hz), 8.47-8.55(1H, m), 11.95(1H, s)

(+)ESI-MS: 439$(M+H)^+$, 461$(M+Na)^+$

Example 4

2-(4-Methyl-1-piperidinyl)-N-[1-(2-pyridinylacetyl)-2,3-dihydro-1H-indol-5-yl]benzamide

The title compound was obtained according to a similar manner to that of Example 1 from 1-(2-pyridinylacetyl)-5-indolinamine and 2-(4-methyl-1-piperidinyl)benzoic acid.

$^1$H-NMR (DMSO-$d_6$):δ 0.93(3H, d, J=6.0 Hz), 1.21-1.62(3H, m), 1.62-1.80(2H, m), 2.67-2.88(2H, m), 3.05-3.27(4H, m), 4.01(2H, s), 4.23(2H, t, J=8.4 Hz), 7.15-7.57(6H, m), 7.70-7.90(3H, m), 8.02(1H, d, J=8.6 Hz), 8.47-8.57(1H, m), 11.63(1H, s)

(+)ESI-MS: 455(M+H)$^+$, 477(M+Na)$^+$

Preparation 3

A mixture of methyl 4-methyl-2-(trifluoromethanesulfonyloxy)benzoate (5.0 g) and pyrrolidine (4.2 ml) in acetonitrile (15.0 ml) was stirred under reflux for 20 hours. The solvent was removed by concentration. The residue was purified by column chromatography on silica gel using a mixture of hexane and ethyl acetate (9:1 v/v) as an eluant. The eluted fractions containing the desired product were collected and evaporated in vacuo to give methyl 4-methyl-2-(1-pyrrolidinyl)benzoate (2.07 g).

$^1$H-NMR (DMSO-$d_6$):δ 1.83-1.90(4H, m), 2.26(3H, s), 3.09-3.16(4H, m), 3.76(3H, s), 6.50(1H, dd, J=0.8 Hz,7.9 Hz), 6.61(1H, d, J=0.8 Hz), 7.33(1H, d, J=7.9 Hz)

(+)APCI-MS: 220(M+H)$^+$

Preparation 4

A mixture of methyl 4-methyl-2-(1-pyrrolidinyl)benzoate (2.0 g) and sodium hydroxide (1.1 g) in a mixture of methanol (30 ml) and water (7.3 ml) was stirred under reflux for 24 hours. The solvent was removed by concentration. To the residue was added a mixture of ethyl acetate, tetrahydrofuran and water and the mixture was adjusted to pH 5.5 with 6N-hydrochloric acid. The separated organic layer was dried over magnesium sulfate and evaporated in vacuo. The residue was triturated with diisopropyl ether to give 4-methyl-2-(1-pyrrolidinyl)benzoic acid (1.48 g).

$^1$H-NMR (DMSO-$d_6$):δ 1.81-1.99(4H, m), 2.29(3H, s), 3.08-3.26(4H, m), 6.66(1H, d, J=7.8 Hz), 6.82(1H, s), 7.50(1H, d, J=7.8 Hz), 13.66(1H, s)

(-)ESI-MS: 204(M-H)$^-$

Example 5

4-Methyl-N-[1-(2-pyridinylacetyl)-2,3-dihydro-1H-indol-5-yl]-2-(1-pyrrolidinyl)benzamide

The title compound was obtained according to a similar manner to that of Example 1 from 1-(2-pyridinylacetyl)-5-indolinamine and 4-methyl-2-(1-pyrrolidinyl)benzoic acid.

$^1$H-NMR (DMSO-$d_6$):δ 1.72-1.94(4H, m), 2.28(3H, s), 3.06-3.29(6H, m), 4.00(2H, s), 4.21(2H, t, J=8.3 Hz), 6.55(1H, d, J=7.7 Hz),

6.60(1H, s), 7.19(1H, d, J=7.7 Hz), 7.23-7.46(3H, m), 7.69(1H, s), 7.71-7.82(1H, m), 7.96(1H, d, J=8.7 Hz), 8.46-8.55(1H, m), 10.23(1H, s)

(-)ESI-MS: 439$(M-H)^-$

Preparation 5

Benzyl 4-methyl-2-(1-piperidinyl)benzoate

The title compound was obtained according to a similar manner to that of Preparation 3 from benzyl 4-methyl-2-(trifluoromethanesulfonyloxy)benzoate and piperidine.

$^1$H-NMR (DMSO-$d_6$):δ 1.38-1.60(6H, m), 2.29(3H, s), 2.82-2.93(4H, m), 5.28(2H, s), 6.78(1H, d, J=8.0 Hz), 6.87(1H, s), 7.29-7.55(6H, m)

Preparation 6

To a mixture of benzyl 4-methyl-2-(1-piperidinyl)benzoate (5.6 g) in methanol (60 ml) was added 10% palladium on carbon (2.0 g, 50% wet). The reaction mixture was stirred at ambient temperature for 5 hours under hydrogen atmosphere. The catalyst was filtered off and the solvent was removed by concentration. The residue was triturated with a mixture of hexane and diisopropyl ether to give 4-methyl-2-(1-piperidinyl)benzoic acid (3.52 g).

$^1$H-NMR (DMSO-$d_6$):δ 1.54-1.83(6H, m), 2.38(3H, s), 2.96-3.10(4H, m), 7.25(1H, d, J=8.0 Hz), 7.56(1H, s), 7.92(1H, d, J=8.0 Hz), 18.13(1H, s)

(-)ESI-MS: 218$(M-H)^-$

Example 6

4-Methyl-2-(1-piperidinyl)-N-[1-(2-pyridinylacetyl)-2,3-dihydro-1H-indol-5-yl]benzamide

The title compound was obtained according to a similar manner to that of Example 1 from 1-(2-pyridinylacetyl)-5-indolinamine and 4-methyl-2-(1-piperidinyl)benzoic acid.

$^1$H-NMR (DMSO-$d_6$):δ 1.45-1.77(6H, m), 2.35(3H, s), 2.86-3.00(4H, m), 3.18(2H, t, J=8.4 Hz), 4.01(2H, s), 4.23(2H, t, J=8.4 Hz), 7.05(1H, d, J=8.0 Hz), 7.17(1H, s), 7.23-7.32(1H, m), 7.32-7.46(2H, m), 7.71-7.87(3H, m), 8.02(1H, d, J=8.7 Hz), 8.47-8.54(1H, m), 11.90(1H, s)

(+)APCI-MS: 455$(M+H)^+$

Preparation 7

Benzyl 4-methyl-2-(4-methyl-1-piperidinyl)benzoate

The title compound was obtained according to a similar manner to that of Preparation 3 from benzyl 4-methyl-2-(trifluoromethanesulfonyloxy)benzoate and 4-methylpiperidine.

$^1$H-NMR (DMSO-$d_6$):δ 0.87(3H, d, J=6.2 Hz), 1.04-1.27(2H, m), 1.27-1.48(1H, m), 1.48-1.62(2H, m), 2.29(3H, s), 2.54-2.71(2H, m), 3.08-3.22(2H, m), 5.27(2H, s), 6.78(1H, d, J=8.0 Hz), 6.87(1H, s), 7.30-7.56(6H, m)

Preparation 8

4-Methyl-2-(4-methyl-1-piperidinyl)benzoic acid

The title compound was obtained according to a similar manner to that of Preparation 6 from benzyl 4-methyl-2-(4-methyl-1-piperidinyl)benzoate.

$^1$H-NMR (DMSO-$d_6$):δ 1.00(3H, d, J=6.4 Hz), 1.20-1.45(2H, m), 1.54-1.77(1H, m), 1.77-1.73(2H, m), 2.38(3H, s), 2.94-3.17(4H, m), 7.24(1H, d, J=8.0 Hz), 7.57(1H, s), 7.92(1H, d, J=8.0 Hz)

(+)ESI-MS: 234$(M+H)^+$

Example 7

4-Methyl-2-(4-methyl-1-piperidinyl)-N-[1-(2-pyridinylacetyl)-2,3-dihydro-1H-indol-5-yl]benzamide

The title compound was obtained according to a similar manner to that of Example 1 from 1-(2-pyridinylacetyl)-5-indolinamine and 4-methyl-2-(4-methyl-1-piperidinyl)benzoic acid.

$^1$H-NMR (DMSO-$d_6$):δ 0.95(3H, d, J=6.0 Hz), 1.18-1.65(3H, m), 1.65-1.80(2H, m), 2.34(3H, s), 2.69-2.86(2H, m), 3.04-3.25(4H, m), 4.01(2H, s), 4.23(2H, t, J=8.4 Hz), 7.04(1H, d, J=8.0 Hz), 7.16(1H, s), 7.24-7.33(1H, m), 7.33-7.43(2H, m), 7.71-7.84(3H, m), 8.02(1H, d, J=8.6 Hz), 8.47-8.54(1H, m), 11.85(1H, s)

(+)ESI-MS: 469$(M+H)^+$, 491$(M+Na)^+$

Preparation 9

Benzyl 2-(4,4-dimethyl-1-piperidinyl)-4-methylbenzoate

The title compound was obtained according to a similar manner to that of Preparation 3 from benzyl 4-methyl-2-(trifluoromethanesulfonyloxy)benzoate and 4,4-dimethylpiperidine.

$^1$H-NMR (DMSO-$d_6$):δ 0.89(6H, s), 1.32(4H, t, J=5.5 Hz), 2.29(3H, s), 2.88(4H, t, J=5.5 Hz), 5.27(2H, s), 6.78(1H, d, J=7.9 Hz),

6.91(1H, s), 7.30-7.54(6H, m)

Preparation 10

2-(4,4-Dimethyl-1-piperidinyl)-4-methylbenzoic acid

The title compound was obtained according to a similar manner to that of Preparation 6 from benzyl 2-(4,4-dimethyl-1-piperidinyl)-4-methylbenzoate.

$^1$H-NMR (DMSO-$d_6$):δ 1.07(6H, s), 7.56(4H, t, J=5.6 Hz), 2.39(3H, s), 3.03(4H, t, J=5.6 Hz), 7.24(1H, d, J=7.9 Hz), 7.71(1H, s), 7.92(1H, d, J=7.9 Hz)

(-)ESI-MS: 246$(M-H)^-$

Example 8

2-(4,4-Dimethyl-1-piperidinyl)-4-methyl-N-[1-(2-pyridinylacetyl)-2,3-dihydro-1H-indol-5-yl]benzamide

The title compound was obtained according to a similar manner to that of Example 1 from 1-(2-pyridinylacetyl)-5-indolinamine and 2-(4,4-dimethyl-1-piperidinyl)-4-methylbenzoic acid.

$^1$H-NMR (DMSO-$d_6$):δ 0.98(6H, s), 1.45-1.59(4H, m), 2.35(3H, s), 2.87-3.00(4H, m), 3.17(2H, t, J=8.4 Hz), 4.01(2H, s), 4.23(2H, t, J=8.4 Hz), 7.04(1H, d, J=8.0 Hz), 7.21-7.33(2H, m), 7.33-7.45(2H, m), 7.71-7.85(3H, m), 8.02(1H, d, J=8.6 Hz), 8.48-8.54(1H, m), 11.92(1H, s)

(+)ESI-MS: 483$(M+H)^+$, 505$(M+Na)^+$

Preparation 11

Benzyl 4-methyl-2-(4-morpholinyl)benzoate

The title compound was obtained according to a similar manner to that of Preparation 3 from benzyl 4-methyl-2-(trifluoromethanesulfonyloxy)benzoate and morpholine.

$^1$H-NMR (DMSO-$d_6$):δ 2.31(3H, s), 2.83-2.96(4H, m), 3.52-3.64(4H, m), 5.28(2H, s), 6.85(1H, d, J=8.0 Hz), 6.90(1H, s), 7.30-7.50(5H, m), 7.58(1H, d, J=8.0 Hz)

Preparation 12

4-Methyl-2-(4-morpholinyl)benzoic acid

The title compound was obtained according to a similar manner to that of Preparation 6 from benzyl 4-methyl-2-(4-morpholinyl)benzoate.

$^1$H-NMR (DMSO-$d_6$):δ 2.38(3H, s), 2.98-3.10(4H, m), 3.73-3.86(4H, m), 7.20(1H, d, J=8.0 Hz), 7.50(1H, s), 7.88(1H, d, J=8.0 Hz),

16.41(1H, s)
(-)ESI-MS: 220(M-H)$^-$

Example 9

4-Methyl-2-(4-morpholinyl)-N-[1-(2-pyridinylacetyl)-2,3-dihydro-1H-indol-5-yl]benzamide

The title compound was obtained according to a similar manner to that of Example 1 from 1-(2-pyridinylacetyl)-5-indolinamine and 4-methyl-2-(4-morpholinyl)benzoic acid.
$^1$H-NMR (DMSO-$d_6$):δ 2.35(3H, s), 2.89-3.04(4H, m), 3.18(2H, t, J=8.3 Hz), 3.65-3.80(4H, m), 4.01(2H, s), 4.22(2H, t, J=8.3 Hz), 7.03(1H, d, J=8.1 Hz), 7.12(1H, s), 7.23-7.33(1H, m), 7.37(1H, d, J=7.7 Hz), 7.43-7.53(1H, m), 7.65-7.84(3H, m), 8.02(1H, d, J=8.7 Hz), 8.47-8.54(1H, m), 11.20(1H, s)
(+)APCI-MS: 457(M+H)$^+$

Preparation 13

Benzyl 4-methyl-2-(4-methyl-1-piperazinyl)benzoate

The title compound was obtained according to a similar manner to that of Preparation 3 from benzyl 4-methyl-2-(trifluoromethanesulfonyloxy)benzoate and 1-methylpiperazine.
$^1$H-NMR (DMSO-$d_6$):δ 2.15(3H, s), 2.25-2.39(4H, m), 2.30(3H, s), 2.86-2.97(4H, m), 5.27(2H, s), 6.81(1H, d, J=8.0 Hz), 6.88(1H, s), 7.31-7.50(5H, m), 7.53(1H, d, J=8.0 Hz)

Preparation 14

4-Methyl-2-(4-methyl-1-piperazinyl)benzoic acid

The title compound was obtained according to a similar manner to that of Preparation 6 from benzyl 4-methyl-2-(4-methyl-1-piperazinyl)benzoate.
$^1$H-NMR (DMSO-$d_6$):δ 2.37(3H, s), 2.46(3H, s), 2.70-2.94(4H, m), 3.06-3.22(4H, m), 7.16(1H, d, J=7.9 Hz), 7.39(1H, s), 7.86(1H, d, J=7.9 Hz), 14.51-17.40(1H, br)
(-)ESI-MS: 233(M-H)$^-$

Example 10

4-Methyl-2-(4-methyl-1-piperazinyl)-N-[1-(2-pyridinylacetyl)-2,3-dihydro-1H-indol-5-yl]benzamide

The title compound was obtained according to a similar manner to that of Example 1 from 1-(2-pyridinylacetyl)-5-indolinamine and 4-methyl-2-(4-methyl-1-piperazinyl)benzoic acid.

$^1$H-NMR (DMSO-$d_6$):δ 2.20(3H, s), 2.35(3H, s), 2.40-2.57(4H, m), 2.90-3.04(4H, m), 3.18(2H, t, J=8.3 Hz), 4.01(2H, s), 4.23(2H, t, J=8.3 Hz), 7.03(1H, d, J=8.0 Hz), 7.14(1H, s), 7.28(1H, dd, J=5.1 Hz,6.8 Hz), 7.33-7.48(2H, m), 7.70-7.85(3H, m), 8.02(1H, d, J=8.7 Hz), 8.47-8.55(1H, m), 11.44(1H, s)

(+)APCI-MS: 470$(M+H)^+$

Preparation 15

Benzyl 4-methyl-2-(4-thiomorpholinyl)benzoate

The title compound was obtained according to a similar manner to that of Preparation 3 from benzyl 4-methyl-2-(trifluoromethanesulfonyloxy)benzoate and thiomorpholine.

$^1$H-NMR (DMSO-$d_6$):δ 2.31(3H, s), 2.55-2.67(4H, m), 3.11-3.22(4H, m), 5.29(2H, s), 6.87(1H, d, J=8.0 Hz), 6.95(1H, s), 7.31-7.52(5H, m), 7.56(1H, d, J=8.0 Hz)

Preparation 16

4-Methyl-2-(4-thiomorpholinyl)benzoic acid

The title compound was obtained according to a similar manner to that of Preparation 6 from benzyl 4-methyl-2-(4-thiomorpholinyl)benzoate.

$^1$H-NMR (DMSO-$d_6$):δ 2.38(3H, s), 2.79-2.92(4H, m), 3.18-3.32(4H, m), 7.21(1H, d, J=8.0 Hz), 7.50(1H, s), 7.89(1H, d, J=8.0 Hz), 16.43(1H, s)

(-)ESI-MS: 236$(M-H)^-$

Example 11

4-Methyl-N-[1-(2-pyridinylacetyl)-2,3-dihydro-1H-indol-5-yl]-2-(4-thiomorpholinyl)benzamide

The title compound was obtained according to a similar manner to that of Example 1 from 1-(2-pyridinylacetyl)-5-indolinamine and 4-methyl-2-(4-thiomorpholinyl)benzoic acid.

$^1$H-NMR (DMSO-$d_6$):δ 2.35(3H, s), 2.68-2.83(4H, m), 3.10-3.30(6H, m), 4.01(2H, s), 4.23(2H, t, J=8.4 Hz), 7.03(1H, d, J=7.9 Hz), 7.12(1H, s), 7.23-7.50(3H, m), 7.68(1H, d, J=7.9 Hz), 7.71-7.84(2H, m), 8.02(1H, d, J=8.6 Hz), 8.47-8.55(1H, m), 11.14(1H, s)

(+)ESI-MS: 473$(M+H)^+$, 495$(M+Na)^+$

Preparation 17

OXONE® (potassium peroxymonosulfate) (2.9 g) was added to a mixture of 4-methyl-2-(4-thiomorpholinyl)benzoic acid

(0.5 g) and tetra-n-butylammonium hydrogensulfate (0.14 g) in a mixture of ethyl acetate (7.5 ml) and water (17.5 ml) and the mixture was stirred at 30°C for 5 hours. The mixture was extracted with ethyl acetate. The extract layer was washed with water, dried over magnesium sulfate and evaporated in vacuo. The residue was triturated with diisopropyl ether to give 2-(1,1-dioxido-4-thiomorpholinyl)-4-methylbenzoic acid (0.18 g).

$^1$H-NMR (DMSO-$d_6$):δ 2.33(3H, s), 3.21-3.37(4H, m), 3.37-3.53(4H, m), 6.99(1H, d, J=7.9 Hz), 7.18(1H, s), 7.71(1H, d, J=7.9 Hz), 13.33(1H, s)

(-)ESI-MS: 268$(M-H)^-$

Example 12

2-(1,1-Dioxido-4-thiomorpholinyl)-4-methyl-N-[1-(2-pyridinylacetyl)-2,3-dihydro-1H-indol-5-yl]benzamide

The title compound was obtained according to a similar manner to that of Example 1 from 1-(2-pyridinylacetyl)-5-indolinamine and 2-(1,1-dioxido-4-thiomorpholinyl)-4-methylbenzoic acid.

$^1$H-NMR (DMSO-$d_6$):δ 2.34(3H, s), 3.08-3.26(6H, m), 3.36-3.50(4H, m), 4.01(2H, s), 4.23(2H, t, J=8.4 Hz), 6.99(1H, d, J=7.9 Hz), 7.09(1H, s), 7.23-7.33(1H, m), 7.33-7.52(3H, m), 7.70-7.85(2H, m), 8.01(1H, d, J=8.7 Hz), 8.46-8.56(1H, m), 10.36(1H, s)

(+)ESI-MS: 505$(M+H)^+$, 527$(M+Na)^+$

Preparation 18

Benzyl 2-(hexahydro-1H-azepin-1-yl)-4-methylbenzoate

The title compound was obtained according to a similar manner to that of Preparation 3 from benzyl 4-methyl-2-(trifluoromethanesulfonyloxy)benzoate and hexamethyleneimine.

$^1$H-NMR (DMSO-$d_6$):δ 1.41-1.55(4H, m), 1.55-1.74(4H, m), 2.26(3H, s), 3.12-3.27(4H, m), 5.26(2H, s), 6.55(1H, d, J=7.5 Hz), 6.77(1H, s), 7.30-7.50(6H, m)

Preparation 19

2-(Hexahydro-1H-azepin-1-yl)-4-methylbenzoic acid

The title compound was obtained according to a similar manner to that of Preparation 6 from benzyl 2-(hexahydro-1H-azepin-1-yl)-4-methylbenzoate.

$^1$H-NMR (DMSO-$d_6$):δ 1.61-1.91(8H, m), 2.37(3H, s), 3.13-3.27(4H,

m), 7.20(1H, d, J=8.0 Hz), 7.48(1H, s), 7.87(1H, d, J=8.0 Hz), 18.19(1H, s)

(-)ESI-MS: 232$(M-H)^-$

Example 13

2-(Hexahydro-1H-azepin-1-yl)-4-methyl-N-[1-(2-pyridinylacetyl)-2,3-dihydro-1H-indol-5-yl]benzamide

The title compound was obtained according to a similar manner to that of Example 1 from 1-(2-pyridinylacetyl)-5-indolinamine and 2-(hexahydro-1H-azepin-1-yl)-4-methylbenzoic acid.

$^1$H-NMR (DMSO-$d_6$):δ 1.52-1.65(4H, m), 1.65-1.84(4H, m), 2.31(3H, s), 3.08-3.29(6H, m), 4.01(2H, s), 4.22(2H, t, J=8.3 Hz), 6.84(1H, d, J=7.6 Hz), 7.01(1H, s), 7.24-7.43(3H, m), 7.51(1H, d, J=7.8 Hz), 7.70-7.83(2H, m), 7.99(1H, d, J=8.7 Hz), 8.47-8.54(1H, m), 11.23(1H, s)

(+)ESI-MS: 469$(M+H)^+$, 491$(M+Na)^+$

Preparation 20

A mixture of 2-fluoro-4-(trifluoromethyl)benzonitrile (5.0 g) and piperidine (7.8 ml) in acetonitrile (25.0 ml) was stirred under reflux for 18 hours. The solvent was removed by concentration. To the residue was added a mixture of ethyl acetate and water, and the mixture was adjusted to pH 2 with 6N-hydorochloric acid. The separated organic layer was washed with water, dried over magnesium sulfate and evaporated in vacuo to give 2-(1-piperidinyl)-4-(trifluoromethyl)-benzonitrile (6.7 g).

$^1$H-NMR (DMSO-$d_6$):δ 2.50-2.77(6H, m), 3.16-3.27(4H, m), 7.30-7.41(2H, m), 7.92(1H, d, J=8.5 Hz)

Preparation 21

A mixture of 2-(1-piperidinyl)-4-(trifluoromethyl)benzonitrile (6.7 g) and sodium hydroxide (2.1 g) in ethylene glycol (27 ml) was stirred at 180°C for 6 hours. After the mixture was added to water (27 ml) at 80°C, the mixture was stirred at 80°C for 1 hour. The reaction mixture was poured into a mixture of ethyl acetate and water, and the mixture was adjusted to pH 3 with 6N-hydrochloric acid. The separated organic layer was washed with water, dried over magnesium sulfate and evaporated in vacuo. The residue was

triturated with diisopropyl ether to give 2-(1-piperidinyl)-4-(trifluoromethyl)benzoic acid (6.5 g).

$^1$H-NMR (DMSO-$d_6$):δ 1.54-1.83(6H, m), 3.06-3.21(4H, m), 7.68(1H, d, J=8.1 Hz), 7.99(1H, s), 8.12(1H, d, J=8.1 Hz), 17.19(1H, s)

(-)ESI-MS: 272(M-H)$^-$

Example 14

2-(1-Piperidinyl)-N-[1-(2-pyridinylacetyl)-2,3-dihydro-1H-indol-5-yl]-4-(trifluoromethyl)benzamide

The title compound was obtained according to a similar manner to that of Example 1 from 1-(2-pyridinylacetyl)-5-indolinamine and 2-(1-piperidinyl)-4-(trifluoromethyl)benzoic acid.

$^1$H-NMR (DMSO-$d_6$):δ 1.40-1.70(6H, m), 2.94-3.07(4H, m), 3.18(2H, t, J=8.4 Hz), 4.01(2H, s), 4.23(2H, t, J=8.4 Hz), 7.28(1H, dd, J=5.0 Hz,6.7 Hz), 7.34-7.52(4H, m), 7.71-7.87(3H, m), 8.02(1H, d, J=8.6 Hz), 8.47-8.54(1H, m), 10.93(1H, s)

(-)ESI-MS: 507(M-H)$^-$

Preparation 22

4-Chloro-2-(1-piperidinyl)benzonitrile

The title compound was obtained according to a similar manner to that of Preparation 20 from 4-chloro-2-fluorobenzonitrile and piperidine.

$^1$H-NMR (DMSO-$d_6$):δ 1.48-1.75(6H, m), 3.08-3.21(4H, m), 7.09(1H, dd, J=1.9 Hz,8.2 Hz), 7.15(1H, d, J=1.9 Hz), 7.70(1H, d, J=8.2 Hz)

Preparation 23

4-Chloro-2-(1-piperidinyl)benzoic acid

The title compound was obtained according to a similar manner to that of Preparation 21 from 4-chloro-2-(1-piperidinyl)benzonitrile.

$^1$H-NMR (DMSO-$d_6$):δ 1.51-1.82(6H, m), 2.98-3.17(4H, m), 7.44(1H, dd, J=2.0 Hz,8.3 Hz), 7.80(1H, d, J=2.0 Hz), 7.97(1H, d, J=8.3 Hz), 17.23(1H, s)

(-)ESI-MS: 238(M-H)$^-$

Example 15

4-Chloro-2-(1-piperidinyl)-N-[1-(2-pyridinylacetyl)-2,3-dihydro-1H-indol-5-yl]benzamide

The title compound was obtained according to a similar

manner to that of Example 1 from 1-(2-pyridinylacetyl)-5-indolinamine and 4-chloro-2-(1-piperidinyl)benzoic acid.

$^1$H-NMR (DMSO-$d_6$):δ 1.04-1.75(6H, m), 2.86-3.03(4H, m), 3.18(2H, t, J=8.4 Hz), 4.01(2H, s), 4.23(2H, t, J=8.4 Hz), 7.17-7.46(5H, m), 7.69-7.84(3H, m), 8.01(1H, d, J=8.6 Hz), 8.46-8.54(1H, m), 11.16(1H, s)

(-)ESI-MS: 473$(M-H)^-$

Preparation 24

4-Methoxy-2-(1-piperidinyl)benzonitrile

The title compound was obtained according to a similar manner to that of Preparation 20 from 2-fluoro-4-methoxybenzonitrile and piperidine.

$^1$H-NMR (DMSO-$d_6$):δ 1.47-1.75(6H, m), 3.03-3.16(4H, m), 3.81(3H, s), 6.57(1H, d, J=2.3 Hz), 6.62(1H, dd, J=2.3 Hz,8.5 Hz), 7.59(1H, d, J=8.5 Hz)

Preparation 25

4-Methoxy-2-(1-piperidinyl)benzoic acid

The title compound was obtained according to a similar manner to that of Preparation 21 from 4-methoxy-2-(1-piperidinyl)benzonitrile.

$^1$H-NMR (DMSO-$d_6$):δ 1.56-1.81(6H, m), 2.97-3.09(4H, m), 3.85(3H, s), 6.99(1H, dd, J=2.5 Hz,8.7 Hz), 7.25(1H, d, J=2.5Hz), 7.97(1H, d, J=8.7 Hz), 17.71(1H, s)

(-)ESI-MS: 234$(M-H)^-$

Example 16

4-Methoxy-2-(1-piperidinyl)-N-[1-(2-pyridinylacetyl)-2,3-dihydro-1H-indol-5-yl]benzamide

The title compound was obtained according to a similar manner to that of Example 1 from 1-(2-pyridinylacetyl)-5-indolinamine and 4-methoxy-2-(1-piperidinyl)benzoic acid.

$^1$H-NMR (DMSO-$d_6$):δ 1.47-1.80(6H, m), 2.85-3.00(4H, m), 3.18(2H, t, J=8.3 Hz), 3.82(3H, s), 4.01(2H, s), 4.22(2H, t, J=8.3 Hz), 6.77-6.88(2H, m), 7.28(1H, dd, J=5.2 Hz,7.1 Hz), 7.34-7.46(2H, m), 7.72-7.85(2H, m), 7.89(1H, d, J=8.3 Hz), 8.02(1H, d, J=8.6 Hz), 8.47-8.56(1H, m), 11.82(1H, s)

(+)ESI-MS: 471$(M+H)^+$, 493$(M+Na)^+$

Preparation 26

Benzyl 5-methyl-2-(1-pyrrolidinyl)benzoate

The title compound was obtained according to a similar manner to that of Preparation 3 from benzyl 5-methyl-2-(trifluoromethanesulfonyloxy)benzoate and pyrrolidine.

$^1$H-NMR (DMSO-$d_6$):δ 1.73-1.90(4H, m), 2.19(3H, s), 2.99-3.13(4H, m), 5.27(2H, s), 6.71(1H, d, J=8.5 Hz), 7.13(1H, dd, J=2.0 Hz,8.5 Hz), 7.27(1H, d, J=2.0 Hz), 7.33-7.50(5H, m)

Preparation 27

5-Methyl-2-(1-pyrrolidinyl)benzoic acid

The title compound was obtained according to a similar manner to that of Preparation 6 from benzyl 5-methyl-2-(1-pyrrolidinyl)benzoate.

$^1$H-NMR (DMSO-$d_6$):δ 1.86-2.01(4H, m), 2.26(3H, s), 3.10-3.25(4H, m), 7.06(1H, d, J=8.4 Hz), 7.25(1H, dd, J=1.8 Hz,8.4 Hz), 7.50(1H, d, J=1.8 Hz), 14.75(1H, s)

(+)ESI-MS: 206$(M+H)^+$, 228$(M+Na)^+$

Example 17

5-Methyl-N-[1-(2-pyridinylacetyl)-2,3-dihydro-1H-indol-5-yl]-2-(1-pyrrolidinyl)benzamide

The title compound was obtained according to a similar manner to that of Example 1 from 1-(2-pyridinylacetyl)-5-indolinamine and 5-methyl-2-(1-pyrrolidinyl)benzoic acid.

$^1$H-NMR (DMSO-$d_6$):δ 1.75-1.94(4H, m), 2.23(3H, s), 3.06-3.25(6H, m), 4.00(2H, s), 4.21(2H, t, J=8.4 Hz), 6.71(1H, d, J=8.2 Hz), 7.05-7.17(2H, m), 7.23-7.46(3H, m), 7.69(1H, s), 7.74(1H, dt, J=1.8 Hz,7.7Hz), 7.97(1H, d, J=8.7 Hz), 8.47-8.54(1H, m), 10.36(1H, s)

(+)ESI-MS: 441$(M+H)^+$, 463$(M+Na)^+$

Preparation 28

Benzyl 5-methyl-2-(1-piperidinyl)benzoate

The title compound was obtained according to a similar manner to that of Preparation 3 from benzyl 5-methyl-2-(trifluoromethanesulfonyloxy)benzoate and piperidine.

$^1$H-NMR (DMSO-$d_6$):δ 1.36-1.59(6H, m), 2.24(3H, s), 2.76-2.88(4H, m), 5.29(2H, s), 6.99(1H, d, J=8.3 Hz), 7.19-7.51(7H, m)

Preparation 29

5-Methyl-2-(1-piperidinyl)benzoic acid

The title compound was obtained according to a similar manner to that of Preparation 6 from benzyl 5-methyl-2-(1-

piperidinyl)benzoate.

$^1$H-NMR (DMSO-$d_6$):δ 1.52-1.87(6H, m), 2.35(3H, s), 2.90-3.14(4H, m), 7.47(1H, d, J=8.2 Hz), 7.62(1H, d, J=8.2 Hz), 7.85(1H, s), 17.20(1H, s)

(+)ESI-MS: 220$(M+H)^+$, 242$(M+Na)^+$

Example 18

5-Methyl-2-(1-piperidinyl)-N-[1-(2-pyridinylacetyl)-2,3-dihydro-1H-indol-5-yl]benzamide

The title compound was obtained according to a similar manner to that of Example 1 from 1-(2-pyridinylacetyl)-5-indolinamine and 5-methyl-2-(1-piperidinyl)benzoic acid

$^1$H-NMR (DMSO-$d_6$):δ 1.46-1.86(6H, m), 2.31(3H, s), 2.82-2.97(4H, m), 3.18(2H, t, J=8.3 Hz), 4.01(2H, s), 4.23(2H, t, J=8.3 Hz), 7.21-7.46(5H, m), 7.71-7.84(3H, m), 8.02(1H, d, J=8.6 Hz), 8.47-8.54(1H, m), 12.06(1H, s)

(+)ESI-MS: 455$(M+H)^+$, 477$(M+Na)^+$

Preparation 30

2-(1-Piperidinyl)-3-(trifluoromethyl)benzonitrile

The title compound was obtained according to a similar manner to that of Preparation 20 from 2-fluoro-3-(trifluoromethyl)benzonitrile and piperidine.

$^1$H-NMR (DMSO-$d_6$):δ 1.46-1.71(6H, m), 2.98-3.21(4H, m), 7.56(1H, t, J=7.7 Hz), 8.02(1H, dd, J=1.4 Hz,7.7 Hz), 8.09(1H, dd, J=1.4 Hz,7.7 Hz)

(+)ESI-MS: 255$(M+H)^+$, 277$(M+Na)^+$

Preparation 31

2-(1-Piperidinyl)-3-(trifluoromethyl)benzoic acid

The title compound was obtained according to a similar manner to that of Preparation 21 from 2-(1-piperidinyl)-3-(trifluoromethyl)benzonitrile.

$^1$H-NMR (DMSO-$d_6$):δ 1.35-1.70(6H, m), 2.87-3.13(4H, m), 7.40(1H, dd, J=7.5 Hz,8.0 Hz), 7.71-7.86(2H, m), 13.45(1H, s)

Example 19

2-(1-Piperidinyl)-N-[1-(2-pyridinylacetyl)-2,3-dihydro-1H-indol-5-yl]-3-(trifluoromethyl)benzamide

The title compound was obtained according to a similar manner to that of Example 1 from 1-(2-pyridinylacetyl)-5-indolinamine and 2-(1-piperidinyl)-3-(trifluoromethyl)benzoic

acid.

$^1$H-NMR (DMSO-$d_6$):δ 1.25-1.63(6H, m), 2.89-3.05(4H, m), 3.18(2H, t, J=8.3 Hz), 4.01(2H, s), 4.23(2H, t, J=8.3 Hz), 7.23-7.33(1H, m), 7.33-7.49(3H, m), 7.61-7.83(4H, m), 8.00(1H, d, J=8.7 Hz), 8.47-8.53(1H, m), 10.45(1H, s)

(-)ESI-MS: 507$(M-H)^-$

Preparation 32

To a solution of 6-methyl-2-pyridinamine (25.0 g) and 2,5-hexanedione (29.0 g) in toluene (150 ml) was added p-toluenesulfonic acid hydrate (4.4 g) at ambient temperature and the mixture was refluxed for 18 hours. The mixture was evaporated in vacuo and the residue was purified by column chromatography on silica gel eluting with n-hexane:ethyl acetate (4:1 v/v) to give 2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-methylpyridine (35.8 g) as a yellow oil.

$^1$H-NMR (DMSO-$d_6$):δ 2.04(6H, s), 2.51(3H, s), 5.78(2H, s), 7.18(1H, d, J=7.8 Hz), 7.29(1H, d, J=7.6 Hz), 7.86(1H, dd, J=7.8 Hz,7.6 Hz)

APCI-MS(m/z): 187$(M+H)^+$

Preparation 33

To a solution of diisopropylamine (11.1 g) in tetrahydrofuran (80 ml) was added dropwise n-butyllithium (1.59M solution in hexane, 69.1 ml) at -60°C under a nitrogen atmosphere and the mixture was stirred at -60°C for 30 minutes. To the mixture was added dropwise a solution of 2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-methylpyridine (18.63 g) in tetrahydrofuran (200 ml) at -60°C over 50 minutes and the reaction mixture was stirred for 30 minutes. Powdered Dry Ice was added carefully and the mixture was gradually warmed to ambient temperature. The mixture was quenched by addition of a saturated aqueous solution of ammonium chloride and poured into a mixture of ethyl acetate and water. The mixture was adjusted to pH 2 with 6N hydrochloric acid. The separated organic layer was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give [6-(2,5-dimethyl-1H-pyrrol-1-yl)-2-pyridinyl]acetic acid (9.69 g) as pale brown crystals.

$^1$H-NMR (DMSO-$d_6$):δ 2.04(6H, s), 3.79(2H, s), 5.79(2H, s), 7.28(2H, d, J=7.9 Hz), 7.38(2H, d, J=7.9 Hz), 7.93(1H, dd, J=7.9 Hz,7.9 Hz), 12.30(1H, br)
ESI-MS(m/z): 253$(M+Na)^+$, 231$(M+H)^+$

Preparation 34

To a solution of 5-nitroindoline (4.925 g), [6-(2,5-dimethyl-1H-pyrrol-1-yl)-2-pyridinyl]acetic acid (8.29 g) and PyBOP (benzotriazol-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (18.7 g) in N,N-dimethylformamide (40 ml) was added dropwise diisopropylethylamine (7.76 g) at 5°C. The mixture was gradually warmed to ambient temperature and stirred for 18 hours. The reaction mixture was poured into a mixture of ethyl acetate and water and the separated organic layer was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel eluting with ethyl acetate to give 1-{[6-(2,5-dimethyl-1H-pyrrol-1-yl)-2-pyridinyl]acetyl}-5-nitroindoline (6.67 g) as light yellow crystals

$^1$H-NMR (DMSO-$d_6$):δ 2.02(6H, s), 3.25(2H, t, J=8.6 Hz), 4.16(2H, s), 4.30(2H, t, J=8.6 Hz), 5.77(2H, s), 7.31(1H, d, J=8.6 Hz), 7.31(1H, d, J=8.6 Hz), 7.98(1H, dd, J=8.6 Hz,8.6 Hz), 8.00-8.15(3H, m)
APCI-MS(m/z): 377$(M+H)^+$

Preparation 35

1-{[6-(2,5-Dimethyl-1H-pyrrol-1-yl)-2-pyridinyl]acetyl}-5-indolinamine

The title compound was obtained according to a similar manner to that of Preparation 2 from 1-{[6-(2,5-dimethyl-1H-pyrrol-1-yl)-2-pyridinyl]acetyl}-5-nitroindoline as light yellow crystals.
$^1$H-NMR (DMSO-$d_6$):δ 2.22(6H, s), 2.99(2H, t, J=8.4 Hz), 3.98(2H, s), 4.08(2H, t, J=8.4 Hz), 4.84(2H, br s), 5.77(2H, s), 6.32(1H, dd, J=8.5 Hz,2.2 Hz), 6.45(1H, d, J=2.2 Hz), 7.27(1H, d, J=7.7 Hz), 7.39(1H, d, J=7.3 Hz), 7.73(1H, d, J=8.5 Hz), 7.94(1H, dd, J=7.7 Hz,7.3 Hz)
ESI-MS(m/z): 369$(M+Na)^+$, 347$(M+H)^+$

Example 20

N-(1-{[6-(2,5-Dimethyl-1H-pyrrol-1-yl)-2-pyridinyl]acetyl}-2,3-dihydro-1H-indol-5-yl)-2-(1-piperidinyl)benzamide

The title compound was obtained according to a similar manner to that of Example 1 from 1-{[6-(2,5-dimethyl-1H-pyrrol-1-yl)-2-pyridinyl]acetyl}-5-indolinamine and 2-(1-piperidinyl)benzoic acid.

$^1$H-NMR (DMSO-$d_6$):δ 1.47-1.75(6H, m), 2.03(6H, s), 2.88-2.99(4H, m), 3.17(2H, t, J=8.4 Hz), 4.07(2H, s), 4.20(2H, t, J=8.4 Hz), 5.77(2H, s), 7.16-7.55(6H, m), 7.79-8.07(4H, m), 11.70(1H, s)

(+)ESI-MS: 534$(M+H)^+$, 556$(M+Na)^+$

Example 21

A mixture of N-(1-{[6-(2,5-dimethyl-1H-pyrrol-1-yl)-2-pyridinyl]acetyl}-2,3-dihydro-1H-indol-5-yl)-2-(1-piperidinyl)benzamide (0.45 g), hydroxylamine hydrochloride (0.59 g) and triethylamine (0.24 ml) in a mixture of ethanol (18 ml) and water (9 ml) was stirred under reflux for 28 hours. The solvent was removed by concentration. To the residue was added a mixture of ethyl acetate, tetrahydrofuran and water and the reaction mixture was adjusted to pH 9 with 20% aqueous potassium carbonate solution. The separated organic layer was washed with water, dried over magnesium sulfate and evaporated in vacuo. The residue was triturated with a mixture of ethyl acetate and tetrahydrofuran to give N-{1-[(6-amino-2-pyridinyl)acetyl]-2,3-dihydro-1H-indol-5-yl}-2-(1-piperidinyl)benzamide (0.11 g).

$^1$H-NMR (DMSO-$d_6$):δ 1.46-1.82(6H, m), 2.88-3.02(4H, m), 3.17(2H, t, J=8.3 Hz), 3.71(2H, s), 4.21(2H, t, J=8.3 Hz), 5.87(2H, s), 6.31(1H, d, J=8.2 Hz), 6.44(1H, d, J=7.1 Hz), 7.16-7.57(5H, m), 7.77-7.90(2H, m), 8.03(1H, d, J=8.6 Hz), 11.68(1H, s)

(-)ESI-MS: 454$(M-H)^-$

Example 22

N-(1-{[6-(2,5-Dimethyl-1H-pyrrol-1-yl)-2-pyridinyl]acetyl}-2,3-dihydro-1H-indol-5-yl)-4-methyl-2-(1-piperidinyl)benzamide

The title compound was obtained according to a similar manner to that of Example 1 from 1-{[6-(2,5-dimethyl-1H-pyrrol-1-yl)-2-pyridinyl]acetyl}-5-indolinamine and 4-methyl-

2-(1-piperidinyl)benzoic acid.

$^1$H-NMR (DMSO-$d_6$):δ 1.48-1.80(6H, m), 2.03(6H, s), 2.35(3H, s), 2.87-3.00(4H, m), 3.17(2H, t, J=8.3 Hz), 4.07(2H, s), 4.20(2H, t, J=8.3 Hz), 5.77(2H, s), 7.05(1H, d, J=8.0 Hz), 7.17(1H, s), 7.30(1H, d, J=7.8 Hz), 7.36-7.47(2H, m), 7.78-7.85(2H, m), 7.91-8.06(2H, m), 11.92(1H, s)

(+)ESI-MS: 548$(M+H)^+$, 570$(M+Na)^+$

Example 23

N-{1-[(6-Amino-2-pyridinyl)acetyl]-2,3-dihydro-1H-indol-5-yl}-4-methyl-2-(1-piperidinyl)benzamide

The title compound was obtained according to a similar manner to that of Example 21 from N-(1-{[6-(2,5-dimethyl-1H-pyrrol-1-yl)-2-pyridinyl]acetyl}-2,3-dihydro-1H-indol-5-yl)-4-methyl-2-(1-piperidinyl)benzamide.

$^1$H-NMR (DMSO-$d_6$):δ 1.46-1.80(6H, m), 2.35(3H, s), 2.84-3.00(4H, m), 3.16(2H, t, J=8.3 Hz), 3.71(2H, s), 4.21(2H, t, J=8.3 Hz), 5.87(2H, s), 6.31(1H, d, J=8.1 Hz), 6.44(1H, d, J=7.2 Hz), 7.05(1H, d, J=7.9 Hz), 7.17(1H, s), 7.26-7.46(2H, m), 7.75-7.87(2H, m), 8.03(1H, d, J=8.6 Hz), 11.90(1H, s)

(-)ESI-MS: 468$(M-H)^-$

Preparation 36

2-Nitrobenzoyl chloride (0.88 g) was added to a mixture of 1-(2-pyridinylacetyl)-5-indolinamine (1.0 g) and triethylamine (0.66 ml) in N,N-dimethylformamide (15 ml) under ice-cooling and the mixture was stirred at ambient temperature for 4 hours. The mixture was poured into a mixture of water and ethyl acetate and the mixture was adjusted to pH 9 with 20% aqueous potassium carbonate solution. The resultant precipitate was collected by filtration to give 2-nitro-N-[1-(2-pyridinylacetyl)-2,3-dihydro-1H-indol-5-yl]benzamide (1.00 g).

$^1$H-NMR (DMSO-$d_6$):δ 3.18(2H, t, J=8.3 Hz), 4.02(2H, s), 4.23(2H, t, J=8.3 Hz), 7.23-7.42(3H, s), 7.65(1H, s), 7.69-7.93(4H, m), 8.00(1H, d, J=8.7 Hz), 8.14(1H, d, J=7.8 Hz), 8.47-8.55(1H, m), 10.61(1H, s)

(-)ESI-MS: 401$(M-H)^-$

Preparation 37

To a mixture of 2-nitro-N-[1-(2-pyridinylacetyl)-2,3-

dihydro-1H-indol-5-yl]benzamide (0.8 g) in a mixture of methanol (30 ml) and tetrahydrofuran (30 ml) was added 10% palladium on carbon (0.4 g, 50% wet). The reaction mixture was stirred at ambient temperature for 5 hours under hydrogen atmosphere. The catalyst was filtered off and the solvent was removed by concentration. The residue was triturated with a mixture of diethyl ether and ethyl acetate to give 2-amino-N-[1-(2-pyridinylacetyl)-2,3-dihydro-1H-indol-5-yl]benzamide (3.52 g).

$^1$H-NMR (DMSO-$d_6$):δ 3.16(2H, t, J=8.3 Hz), 4.01(2H, s), 4.22(2H, t, J=8.3 Hz), 6.31(2H, s), 6.53-6.63(1H, m), 6.70-6.77(1H, m), 7.14-7.32(2H, m), 7.33-7.47(2H, m), 7.60(1H, dd, J=1.1 Hz,7.9 Hz), 7.66(1H, s), 7.77(1H, dt, J=1.8 Hz,7.6 Hz), 7.98(1H, d, J=8.7 Hz), 8.48-8.54(1H, m), 9.93(1H, s)

(-)ESI-MS: 371$(M-H)^-$

Example 24

2-(Dimethylamino)-N-[1-(2-pyridinylacetyl)-2,3-dihydro-1H-indol-5-yl]benzamide

The title compound was obtained according to a similar manner to that of Example 1 from 1-(2-pyridinylacetyl)-5-indolinamine and 2-(dimethylamino)benzoic acid.

$^1$H-NMR (DMSO-$d_6$):δ 2.77(6H, s), 3.17(2H, t, J=8.4 Hz), 4.01(2H, s), 4.22(2H, t, J=8.4 Hz), 7.04-7.15(1H, m), 7.18-7.50(5H, m), 7.64-7.83(3H, m), 8.00(1H, d, J=8.7 Hz), 8.47-8.54(1H, m), 11.25(1H, s)

(+)APCI-MS: 401$(M+H)^+$

Preparation 38

To a mixture of 2-amino-4-methylbenzoic acid (3.0 g) and 37% aqueous formaldehyde (29.7 ml) in methanol (60 ml) was added 10% palladium on carbon (2.0 g, 50% wet). The reaction mixture was stirred at ambient temperature for 16 hours under hydrogen atmosphere. The catalyst was filtered off and the solvent was removed by concentration and the residue was triturated with ethyl acetate to give 2-(dimethylamino)-4-methylbenzoic acid (1.91 g).

$^1$H-NMR (DMSO-$d_6$):δ 2.38(3H, s), 2.80(6H, s), 7.20(1H, d, J=7.9 Hz), 7.56(1H, s), 7.88(1H, d, J=7.9 Hz)

(+)ESI-MS: 180$(M+H)^+$, 202$(M+Na)^+$

Example 25

2-(Dimethylamino)-4-methyl-N-[1-(2-pyridinylacetyl)-2,3-dihydro-1H-indol-5-yl]benzamide

The title compound was obtained according to a similar manner to that of Example 1 from 1-(2-pyridinylacetyl)-5-indolinamine and 2-(dimethylamino)-4-methylbenzoic acid.

$^1$H-NMR (DMSO-$d_6$):δ 2.34(3H, s), 2.76(6H, s), 3.17(2H, t, J=8.3 Hz), 4.01(2H, s), 4.22(2H, t, J=8.3 Hz), 6.95(1H, t, J=8.0 Hz), 7.10(1H, s), 7.24-7.47(3H, m), 7.64-7.82(3H, m), 8.00(1H, d, J=8.6 Hz), 8.48-8.53(1H, m), 11.50(1H, s)

(+)ESI-MS: 415$(M+H)^+$, 437$(M+Na)^+$

Preparation 39

A mixture of 2-chloro-6-methylnicotinic acid (3.43 g), tert-butyl 5-amino-1-indolinecarboxylate (5.15 g), 1-hydroxybenzotriazole hydrate (3.21 g) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (3.26 g) in N,N-dimethylformamide (30 ml) was stirred at ambient temperature overnight. The reaction mixture was poured into a mixture of ethyl acetate and water, and the organic layer was washed with brine and dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was chromatographed on silica gel eluting with ethyl acetate and n-hexane (6:4 v/v). The eluted fractions containing the desired product were collected and evaporated in vacuo to give tert-butyl 5-{[(2-chloro-6-methyl-3-pyridinyl)carbonyl]amino}-1-indolinecarboxylate (6.65 g).

$^1$H-NMR (DMSO-$d_6$):δ 1.51(9H, s), 2.51(3H, s), 3.07(2H, t, J=8.5 Hz), 3.91(2H, t, J=8.5 Hz), 7.37-7.41(2H, m), 7.52-7.69(2H, m), 7.92(1H, d, J=7.6 Hz), 10.43 (1H, s)

Preparation 40

A mixture of tert-butyl 5-{[(2-chloro-6-methyl-3-pyridinyl)carbonyl]amino}-1-indolinecarboxylate (1.55 g) and piperidine (1.6 ml) in tetrahydrofuran (10 ml) was refluxed under stirring for 4.5 hours. The reaction mixture was poured into a mixture of ethyl acetate and water, and the organic layer was washed with brine and dried over magnesium sulfate. The solvent was concentrated in vacuo and the precipitate was collected by filtration to give tert-butyl 5-({[6-methyl-2-(1-

piperidinyl)-3-pyridinyl]carbonyl}amino)-1-indolinecarboxylate (1.01 g).

$^1$H-NMR (DMSO-$d_6$):δ 1.51(9H, s), 1.51-1.53(6H, m), 2.40(3H, s), 3.35(2H, t, J=8.4 Hz), 3.35(4H, m), 3.90(2H, t, J=8.4 Hz), 6.83(1H, d, J=7.7 Hz), 7.40-7.43(2H, m), 7.67(1H, s), 7.75(1H, d, J=7.6 Hz), 10.47(1H, s)

(+)ESI-MS(m/z): 437$(M+H)^+$, 459$(M+Na)^+$

Preparation 41

A mixture of tert-butyl 5-({[6-methyl-2-(1-piperidinyl)-3-pyridinyl]carbonyl}amino)-1-indolinecarboxylate (1.0 g) and trifluoroacetic acid (1.8 ml) in dichloromethane (5 ml) was stirred at ambient temperature for 5 hours. The reaction mixture was evaporated in vacuo. The residue was dissolved in a mixture of ethyl acetate and water and the mixture was adjusted to pH 8.5 with aqueous potassium carbonate solution. The organic layer was washed with brine and dried over magnesium sulfate. The solvent was concentrated in vacuo and the precipitate was collected by filtration to give N-(2,3-dihydro-1H-indol-5-yl)-6-methyl-2-(1-piperidinyl)nicotinamide (595 mg).

$^1$H-NMR (DMSO-$d_6$):δ 1.52-1.58(6H, m), 2.39(3H, s), 2.90(2H, t, J=8.4 Hz), 3.19-3.21(4H, m), 3.35-3.42(2H, m), 5.35(1H, s), 6.46(1H, d, J=8.3 Hz), 6.83(1H, d, J=7.6 Hz), 7.20(1H, d, J=8.3 Hz), 7.417(1H, s), 7.75(1H, d, J=7.6 Hz), 10.29(1H, s)

Example 26

A mixture of N-(2,3-dihydro-1H-indol-5-yl)-6-methyl-2-(1-piperidinyl)nicotinamide (330 mg), 2-pyridylacetic acid dihydrochloride (179 mg), 1-hydroxybenzotriazole hydrate (158 mg), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (160 mg) and N,N-dimethylaminopyridine (2.4 mg) in N,N-dimethylformamide (15 ml) was stirred at ambient temperature overnight. The reaction mixture was poured into a mixture of ethyl acetate and water and the organic layer was washed with brine and dried over magnesium sulfate. The solvent was concentrated in vacuo and the precipitate was collected by filtration to give 6-methyl-2-(1-piperidinyl)-N-[1-(2-pyridinylacetyl)-2,3-dihydro-1H-indol-5-yl]nicotinamide (305 mg).

$^1$H-NMR (DMSO-$d_6$):δ 1.53(6H, br,s), 2.39(3H, s), 3.13-3.55(8H, m), 4.01(2H, s), 4.22(2H, t, J=8.30 Hz), 6.83(1H, d, J=7.64 Hz), 7.24-7.43(3H, m), 7.73-7.81(3H, m), 7.89(1H, d, J=8.66 Hz), 8.48-8.51(1H, m), 10.52(1H, s)
(+)ESI-MS(m/z): 456$(M+H)^+$, 478$(M+Na)^+$

Preparation 42

tert-Butyl 5-({[6-methyl-2-(4-methyl-1-piperidinyl)-3-pyridinyl]carbonyl}amino)-1-indolinecarboxylate

The title compound was obtained according to a similar manner to that of Preparation 40 from tert-butyl 5-{[(2-chloro-6-methyl-3-pyridinyl)carbonyl]amino}-1-indolinecarboxylate and 4-methylpiperidine.

$^1$H-NMR (DMSO-$d_6$):δ 0.98(3H, d, J=6.2 Hz), 1.13-1.28(2H, m), 1.40(9H, s), 1.40-1.65(3H, m), 2.39(3H, s), 2.74-2.80(2H, m), 3.10(2H, t, J=8.4 Hz), 3.60-3.68(2H, m), 3.90(2H, t, J=8.4 Hz), 6.82(1H, d, J=7.6 Hz), 7.39-7.42(1H, m), 7.42-7.67(1H, m), 7.67(1H, s), 7.74(1H, d, J=7.6 Hz), 10.44(1H, s)
(+)ESI-MS(m/z): 451$(M+H)^+$, 473$(M+Na)^+$

Preparation 43

N-(2,3-Dihydro-1H-indol-5-yl)-6-methyl-2-(4-methyl-1-piperidinyl)nicotinamide

The title compound was obtained according to a similar manner to that of Preparation 41 from tert-butyl 5-({[6-methyl-2-(4-methyl-1-piperidinyl)-3-pyridinyl]carbonyl}amino)-1-indolinecarboxylate.

$^1$H-NMR (DMSO-$d_6$):δ 0.90(3H, d, J=6.1 Hz), 1.18-1.31(2H, m), 1.46-1.66(3H, m), 2.38(3H, s), 2.74-2.94(4H, m), 3.33-3.44(2H, m), 3.60-3.67(2H, m), 5.34(1H, s), 6.46(1H, d, J=8.2 Hz), 6.82(1H, d, J=7.6 Hz), 7.20(1H, dd, J=1.9 Hz,8.2 Hz), 7.46(1H, d, J=1.9 Hz), 7.74(1H, d, J=7.6 Hz), 10.24(1H, s)
(+)ESI-MS(m/z): 351$(M+H)^+$, 373$(M+Na)^+$

Example 27

6-Methyl-2-(4-methyl-1-piperidinyl)-N-[1-(2-pyridinylacetyl)-2,3-dihydro-1H-indol-5-yl]nicotinamide

The title compound was obtained according to a similar manner to that of Example 26 from N-(2,3-dihydro-1H-indol-5-yl)-6-methyl-2-(4-methyl-1-piperidinyl)nicotinamide and 2-pyridylacetic acid dihydrochloride.

$^1$H-NMR (DMSO-$d_6$):δ 0.88(3H, d, J=6.1 Hz), 1.14-1.21(2H, m), 1.52-1.70(3H, m), 2.39(3H, s), 2.70-2.80(2H, m), 3.17-3.21(2H, m), 3.61-3.68(2H, m), 4.00(2H, s), 4.12-4.22(2H, m), 6.82(1H, d, J=7.6 Hz), 7.28-7.42(3H, m), 7.72-7.77(3H, m), 7.98 (1H, d, J=8.7 Hz), 8.49-8.52(1H, m), 10.47(1H, s)

(+)ESI-MS(m/z): 470$(M+1)^+$, 492$(M+Na)^+$

Preparation 44

A mixture of 2-chloro-nicotinic acid (1.58 g), 1-(2-pyridinylacetyl)-5-indolinamine (2.67 g), 1-hydroxybenzotriazole hydrate (1.61 g) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (1.63 g) in N,N-dimethylformamide (30 ml) was stirred at ambient temperature overnight. The reaction mixture was poured into a mixture of ethyl acetate and water and stirred at ambient temperature for 20 minutes. The precipitate was collected by filtration and washed successively with water, ethyl acetate and diisopropyl ether and dried to give 2-chloro-N-[1-(2-pyridinylacetyl)-2,3-dihydro-1H-indol-5-yl]nicotinamide (2.95 g).

$^1$H-NMR (DMSO-$d_6$):δ 3.18(2H, t, J=8.32 Hz), 4.01(2H, s), 4.23(2H, t, J=8.32 Hz), 7.25-7.39(1H, m), 7.52-7.59(2H, m), 7.68-7.69(1H, m), 7.76-7.77(2H, m), 7.97-8.08(2H, m), 8.49-8.54(2H, m), 10.57(1H, s)

Example 28

A mixture of 2-chloro-N-[1-(2-pyridinylacetyl)-2,3-dihydro-1H-indol-5-yl]nicotinamide (432 mg) and piperidine (0.45 ml) in chloroform (20 ml) was refluxed under stirring for 12 hours. The reaction mixture was poured into a mixture of chloroform and water and the organic layer was washed with brine and dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was chromatographed on silica gel eluting with chloroform and methanol (97:3 v/v). The fractions containing the desired product were collected and concentrated in vacuo and the precipitate was collected by filtration to give 2-(1-piperidinyl)-N-[1-(2-pyridinylacetyl)-2,3-dihydro-1H-indol-5-yl]nicotinamide (335 mg).

$^1$H-NMR (DMSO-$d_6$):δ 1.53(6H, s), 3.22-3.25(4H, m), 4.01(2H, s), 6.90-6.98(1H, m), 7.21-7.43(3H, m), 7.70-7.82(3H, m), 7.96-8.02(1H, m), 8.23-8.26(1H, m), 8.45-8.47(1H, m), 10.46(1H, s)

(+)ESI-MS(m/z): 442 $(M+H)^+$, 464 $(M+Na)^+$

Example 29

2-(4-Methyl-1-piperidinyl)-N-[1-(2-pyridinylacetyl)-2,3-dihydro-1H-indol-5-yl]nicotinamide

The title compound was obtained according to a similar manner to that of Example 28 from 2-chloro-N-[1-(2-pyridinylacetyl)-2,3-dihydro-1H-indol-5-yl]nicotinamide and 4-methylpiperidine.

$^1$H-NMR (DMSO-$d_6$):δ 0.87(3H, d, J=6.1 Hz), 1.14-1.21(2H, m), 1.21-1.64(3H, m), 2.76-2.88(2H, m), 3.17(2H, t, J=8.3 Hz), 3.66-3.73(2H, m), 4.01(2H, s), 4.22(2H, t, J=8.3 Hz), 6.90-6.96(1H, m), 7.28-7.34(3H, m), 7.72-7.82(3H, m), 7.98(1H, d, J=8.6 Hz), 8.26-8.29(1H, m), 8.49-8.51(1H, m), 10.45(1H, s)

(+)ESI-MS(m/z): 456 $(M+H)^+$, 478 $(M+Na)^+$

Preparation 45

2-Chloro-N-(2,3-dihydro-1H-indol-5-yl)-6-methylnicotinamide

The title compound was obtained according to a similar manner to that of Preparation 41 from tert-butyl 5-{[(2-chloro-6-methyl-3-pyridinyl)carbonyl]amino}-1-indolinecarboxylate.

$^1$H-NMR (DMSO-$d_6$):δ 2.50(3H, s), 2.90(2H, t, J=8.3 Hz), 3.34-3.45(2H, m), 5.39(1H, s), 6.46(1H, d, J=8.3 Hz), 7.18(1H, dd, J=1.9 Hz,8.3 Hz), 7.35-7.40(2H, m), 7.88(1H, d, J=7.6 Hz), 10.13(1H, s)

Preparation 46

2-Chloro-6-methyl-N-[1-(2-pyridinylacetyl)-2,3-dihydro-1H-indol-5-yl]nicotinamide

The title compound was obtained according to a similar manner to that of Preparation 41 from 2-chloro-N-(2,3-dihydro-1H-indol-5-yl)-6-methylnicotinamide and 2-pyridylacetic acid dihydrochloride.

$^1$H-NMR (DMSO-$d_6$):δ 2.50(3H, s), 3.20(2H, t, J=8.3 Hz), 3.96(2H, s), 4.23(2H, t, J=8.3 Hz), 7.27-7.28(1H, m), 7.36-7.41(3H, m), 7.67 (1H, s), 7.74-7.78(1H, m), 7.98-8.00(1H, m), 8.80(1H, d, J=3.4 Hz), 10.46(1H, s)

Example 30

6-Methyl-N-[1-(2-pyridinylacetyl)-2,3-dihydro-1H-indol-

5-yl]-2-(4-morpholinyl)nicotinamide

The title compound was obtained according to a similar manner to that of Example 28 from 2-chloro-6-methyl-N-[1-(2-pyridinylacetyl)-2,3-dihydro-1H-indol-5-yl]nicotinamide and morpholine.

$^1$H-NMR (DMSO-$d_6$):δ 2.49(3H, s), 3.13-3.34(6H, m), 3.61-3.66(4H, m), 3.94(2H, s), 4.22(2H, t, J=8.3 Hz), 6.85(1H, d, J=7.6 Hz), 7.25-7.45(3H, m), 7.71-7.81(3H, m), 7.94-8.17(1H, m), 8.80(1H, d, J=3.9 Hz), 10.39(1H, s)

(+)ESI-MS(m/z): 458$(M+H)^+$, 480$(M+Na)^+$

Example 31

A mixture of N-(2,3-dihydro-1H-indol-5-yl)-6-methyl-2-(1-piperidinyl)nicotinamide (286 mg), {6-[(tert-butoxycarbonyl)amino]-2-pyridinyl}acetic acid (225 mg), 1-hydroxybenzotriazole hydrate (137 mg, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (139 mg) and N,N-dimethylaminopyridine (2.4 mg) in N,N-dimethylformamide (15 ml) was stirred at ambient temperature overnight. The reaction mixture was poured into a mixture of ethyl acetate and water and the organic layer was washed with brine and dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was chromatographed on silica gel eluting with ethyl acetate and n-hexane (7:3 v/v). The fractions containing the desired product were collected and evaporated in vacuo to give tert-butyl 6-{2-[5-({[6-methyl-2-(1-piperidinyl)-3-pyridinyl]carbonyl}amino)-2,3-dihydro-1H-indol-1-yl]-2-oxoethyl}-2-pyridinylcarbamate (470 mg).

$^1$H-NMR (DMSO-$d_6$):δ 1.46(9H, s), 1.53(6H, br.s), 2.39(3H, s), 3.14-3.33(6H, m), 6.83(1H, d, J=7.7 Hz), 6.96-7.00(1H, m), 7.37-7.42(1H, m), 7.67-7.77(4H, m), 7.98(1H, d, J=8.7 Hz), 9.67(1H, s), 10.52(1H, s)

Example 32

A mixture of tert-butyl 6-{2-[5-({[6-methyl-2-(1-piperidinyl)-3-pyridinyl]carbonyl}amino)-2,3-dihydro-1H-indol-1-yl]-2-oxoethyl}-2-pyridinylcarbamate (460 mg) and trifluoroacetic acid (0.6 ml) in dichloromethane (5 ml) was stirred at ambient temperature for 5 hours. The reaction mixture was evaporated in vacuo and the residue was dissolved

in a mixture of ethyl acetate and water and adjusted to pH 8.5 with aqueous potassium carbonate solution. The organic layer was washed with brine and dried over magnesium sulfate. The solvent was concentrated in vacuo and the precipitate was collected by filtration to give N-{1-[(6-amino-2-pyridinyl)acetyl]-2,3-dihydro-1H-indol-5-yl}-6-methyl-2-(1-piperidinyl)nicotinamide (306 mg).

$^1$H-NMR (DMSO-$d_6$):δ 1.53(6H, br.s), 2.39(3H, s), 3.11-3.30(6H, m), 4.20(2H, t, J=8.3 Hz), 5.86(2H, s), 6.30(1H, d, J=7.9 Hz), 6.43(1H, d, J=7.0 Hz), 6.83(1H, d, J=7.6 Hz), 7.28-7.43(2H, m), 7.72-7.78(2H, m), 7.98(1H, d, J=8.7 Hz), 10.51(1H, s)

(+)ESI-MS(m/z): 471$(M+H)^+$

Preparation 47

A mixture of tert-butyl 5-{[(2-chloro-6-methyl-3-pyridinyl)carbonyl]amino}-1-indolinecarboxylate (3.1 g) in 2M dimethylamine-tetrahydrofuran solution (20 ml) was refluxed under stirring for 10 hours. The reaction mixture was poured into a mixture of ethyl acetate and water and the organic layer was washed with brine and dried over magnesium sulfate. The solvent was concentrated in vacuo and the precipitate was collected by filtration to give tert-butyl 5-({[2-(dimethylamino)-6-methyl-3-pyridinyl]carbonyl}amino)-1-indolinecarboxylate (2.19 g).

$^1$H-NMR (DMSO-$d_6$):δ 1.51(9H, s), 2.36(3H, s), 2.94(6H, s), 3.05 (2H, t, J=8.4 Hz), 3.90(2H, t, J=8.4 Hz), 6.61(1H, d, J=7.5 Hz), 7.39-7.43(1H, m), 7.54-7.60(3H, m), 10.18(1H, s)

(+)ESI-MS(m/z): 397$(M+H)^+$, 419$(M+Na)^+$

Preparation 48

N-(2,3-Dihydro-1H-indol-5-yl)-2-(dimethylamino)-6-methylnicotinamide

The title compound was obtained according to a similar manner to that of Preparation 41 from tert-butyl 5-({[2-(dimethylamino)-6-methyl-3-pyridinyl]carbonyl}amino)-1-indolinecarboxylate.

$^1$H-NMR (DMSO-$d_6$):δ 2.35(3H, s), 2.89(2H, t, J=8.4 Hz), 2.94(6H, s), 3.39(2H, t, J=8.4 Hz), 5.33(1H, s), 6.43(1H, d, J=7.5 Hz), 6.60(1H, d, J=7.5 Hz), 7.18(1H, m), 7.40(1H, s), 7.53(1H, d, J=7.4 Hz), 9.90(1H, s)

(+)ESI-MS(m/z): 297$(M+H)^+$

Example 33

tert-Butyl 6-{2-[5-({[2-(dimethylamino)-6-methyl-3-pyridinyl]carbonyl}amino)-2,3-dihydro-1H-indol-1-yl]-2-oxoethyl}-2-pyridinylcarbamate

The title compound was obtained according to a similar manner to that of Example 31 from N-(2,3-dihydro-1H-indol-5-yl)-2-(dimethylamino)-6-methylnicotinamide and {6-[(tert-butoxycarbonyl)amino]-2-pyridinyl}acetic acid.

$^1$H-NMR (DMSO-$d_6$):δ 1.46(9H, s), 2.36(3H, s), 2.89(6H, s), 3.17(2H, t, J=8.3 Hz), 3.86(2H, s), 4.27(2H, t, J=8.3 Hz), 6.61(1H, d, J=7.5 Hz), 6.96-7.00(1H, m), 7.35-7.40(1H, m), 7.57(1H, d, J=7.5 Hz), 7.64-7.69(2H, m), 7.94-7.98(2H, m), 9.67(1H, s), 10.23(1H, s)

(+)ESI-MS(m/z): 531$(M+H)^+$, 553$(M+Na)^+$

Example 34

N-{1-[(6-Amino-2-pyridinyl)acetyl]-2,3-dihydro-1H-indol-5-yl}-2-(dimethylamino)-6-methylnicotinamide

The title compound was obtained according to a similar manner to that of Example 32 from tert-butyl 6-{2-[5-({[2-(dimethylamino)-6-methyl-3-pyridinyl]carbonyl}amino)-2,3-dihydro-1H-indol-1-yl]-2-oxoethyl}-2-pyridinylcarbamate.

$^1$H-NMR (DMSO-$d_6$):δ 2.35(3H, s), 2.94(6H, s), 3.14(2H, t, J=8.4 Hz), 3.71(2H, s), 4.19(2H, t, J=8.4 Hz), 5.87(2H, s), 6.31(1H, d, J=8.2 Hz), 6.43(1H, d, J=7.2 Hz), 6.61 (1H, d, J=7.5 Hz), 7.30-7.40(2H, m), 7.57(1H, d, J=7.5 Hz), 7.66(1H, s), 7.98(1H, d, J=8.7 Hz), 10.22(1H, s)

(+)ESI-MS(m/z): 431$(M+H)^+$, 453$(M+Na)^+$

Example 35

2-(Dimethylamino)-6-methyl-N-[1-(2-pyridinylacetyl)-2,3-dihydro-1H-indol-5-yl]nicotinamide

The title compound was obtained according to a similar manner to that of Example 26 from N-(2,3-dihydro-1H-indol-5-yl)-2-(dimethylamino)-6-methylnicotinamide and 2-pyridylacetic acid dihydrochloride.

$^1$H-NMR (DMSO-$d_6$):δ 2.37(3H, s), 2.95(6H, s), 3.19(2H, t, J=8.4 Hz), 3.92(2H, s), 3.93(2H, t, J=8.4 Hz), 6.63(1H, d, J=7.6 Hz), 7.51-7.62(2H, m), 7.73-7.82(2H, m), 7.91(1H, d, J=8.6 Hz),

8.11-8.23(2H, m), 8.79-8.81(1H, m), 10.34(1H, s)

Example 36

1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide (0.19 g) was added to a solution of N-(4-aminophenyl)-2-(2-pyridinyl)acetamide (0.23 g), 4-methyl-2-(4-methyl-1-piperidinyl)benzoic acid (0.28 g), 1-hydroxybenzotriazole hydrate (0.16 g) and 4-dimethylaminopyridine (6 mg) in dichloromethane (5 ml) under ice-cooling and the mixture was stirred at ambient temperature for 18 hours. The reaction mixture was poured into a mixture of ethyl acetate and water. The separated organic layer was washed with water, dried over magnesium sulfate and evaporated in vacuo. The residue was triturated with ethyl acetate to give 4-methyl-2-(4-methyl-1-piperidinyl)-N-{4-[(2-pyridinylacetyl)amino]phenyl}benzamide (0.14 g).

$^1$H-NMR (DMSO-$d_6$):δ 0.95(3H, d, J=6.0 Hz), 1.20-1.62(3H, m), 1.67-1.82(2H, m), 2.35(3H, s), 2.69-2.87(2H, m), 3.04-3.17(2H, m), 3.84(2H, s), 7.04(1H, d, J=7.9 Hz), 7.17(1H, s), 7.23-7.32(1H, m), 7.41(1H, d, J=7.8 Hz), 7.60(2H, d, J=9.1 Hz), 7.69(2H, d, J=9.1 Hz), 7.69-7.86(2H, m), 8.48-8.54(1H, m), 10.23(1H, s), 11.87(1H, s)

(+)ESI-MS: 443$(M+H)^+$, 465$(M+Na)^+$

Example 37

2-(Dimethylamino)-4-methyl-N-{4-[(2-pyridinylacetyl)amino]phenyl}benzamide

The title compound was obtained according to a similar manner to that of Example 36 from N-(4-aminophenyl)-2-(2-pyridinyl)acetamide and 2-(dimethylamino)-4-methylbenzoic acid.

$^1$H-NMR (DMSO-$d_6$):δ 2.34(3H, s), 2.76(6H, s), 3.84(2H, s), 6.95(1H, d, J=7.8 Hz), 7.10(1H, s), 7.22-7.32(1H, m), 7.40(1H, d, J=7.8 Hz), 7.53-7.83(6H, m), 8.47-8.54(1H, m), 10.22(1H, s), 11.51(1H, s)

(+)ESI-MS: 389$(M+H)^+$, 411$(M+Na)^+$

Preparation 49

To a solution of 4-fluoronitrobenzene (12.71 g) and 2-(2-pyridinyl)ethylamine (12.22 g) in N,N-dimethylformamide (70 ml) was added triethylamine (10.12 g) at ambient temperature and the mixture was stirred at 60°C for 16 hours. The mixture

was cooled to 5°C and poured into a mixture of ethyl acetate and water. The separated organic layer was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was triturated with diisopropyl ether, collected by filtration, washed with diisopropyl ether and dried in vacuo to give 2-[2-(4-nitroanilino)ethyl]pyridine (21.21 g) as a yellow solid.

$^1$H-NMR(DMSO-$d_6$):δ 3.02(2H, t, J=7.0 Hz), 3.55(2H, td, J=7.0 Hz, 5.6 Hz), 6.65(2H, d, J=9.3 Hz), 7.24(1H, dd, J=7.8 Hz,4.9 Hz), 7.31(1H, d, J=7.8 Hz), 7.39(1H, t, J=5.6 Hz), 7.65-7.8(1H, m), 7.98(1H, d, J=9.3 Hz), 8.52(1H, d, J=4.0 Hz)

APCI-MS(m/z): 244($M^+$+1)

Preparation 50

To a solution of 2-[2-(4-nitroanilino)ethyl]pyridine (17.87 g) in tetrahydrofuran (150 ml) were added di-tert-butyl dicarbonate (19.25 g) and triethylamine (8.92 g) at ambient temperature and the mixture was refluxed for 16 hours. The mixture was evaporated in vacuo and the residue was purified by column chromatography on silica gel eluting with hexane:ethyl acetate (2:1 v/v) to give tert-butyl 4-nitrophenyl[2-(2-pyridinyl)ethyl]carbamate (18.21 g) as a yellow solid.

$^1$H-NMR(DMSO-$d_6$):δ 1.37(9H, s), 2.95(2H, t, J=8.0 Hz), 4.09(2H, t, J=8.0 Hz), 7.2-7.3(2H, m), 7.52(2H, d, J=9.1 Hz), 7.65-7.75(1H, m), 8.17(2H, d, J=9.1 Hz), 8.23(1H, d, J=4.8 Hz)

APCI-MS(m/z): 344($M^+$+1)

Preparation 51

To a suspension of tert-butyl 4-nitrophenyl[2-(2-pyridinyl)ethyl]carbamate (20.03 g) in ethanol (400 ml) were added iron(III) chloride (anhydrous) (189 mg) and active-charcoal (20 g) and the mixture was heated to 80°C. To the mixture was added dropwise hydrazine hydrate (11.67 g) and the mixture was stirred at 80°C for 4 hours. The active-charcoal was filtered off by celite and washed with ethanol. The filtrate was evaporated in vacuo and the residue was purified by column chromatography on silica gel eluting with ethyl acetate to give tert-butyl 4-aminophenyl[2-(2-pyridinyl)ethyl]carbamate (15.03 g) as a light brown solid.

$^1$H-NMR(DMSO-$d_6$):δ 1.29(9H, s), 2.86(2H, t, J=7.0 Hz), 3.78(2H, t, J=7.0 Hz), 5.04(2H, br s), 6.52 (2H, d, J=8.5 Hz), 6.80(2H, d, J=8.5 Hz), 7.15-7.3(2H, m), 7.65-7.75(1H, m), 8.45(1H, d, J=4.2 Hz)

APCI-MS(m/z): 314$(M+H)^+$

Example 38

1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide (0.19 g) was added to a solution of tert-butyl 4-aminophenyl[2-(2-pyridinyl)ethyl]carbamate (0.31 g), 4-methyl-2-(1-pyrrolidinyl)benzoic acid (0.25 g), 1-hydroxybenzotriazole hydrate (0.16 g) and 4-dimethylaminopyridine (6 mg) in dichloromethane (5 ml) under ice-cooling and the mixture was stirred at ambient temperature for 18 hours. To the reaction mixture was added a solution of 10% hydrogen chloride in methanol (9 ml) and the mixture was stirred at ambient temperature for 20 hours. The reaction mixture was poured into a mixture of ethyl acetate and water, and the mixture was adjusted to pH 9 with 20% aqueous potassium carbonate solution. The separated organic layer was washed with water, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel using a mixture of ethyl acetate and diisopropyl ether (1:1 v/v) as an eluant. The eluted fractions containing the desired product were collected and evaporated in vacuo to give 4-methyl-N-(4-{[2-(2-pyridinyl)ethyl]amino}phenyl)-2-(1-pyrrolidinyl)benzamide (0.18 g).

$^1$H-NMR(DMSO-$d_6$):δ 1.77-1.93(4H, m), 2.27(3H, s), 2.98(2H, t, J=7.2 Hz), 3.14-3.28(4H, m), 3.28-3.43(2H, m), 5.51(1H, t, J=5.7 Hz), 6.50-6.64(4H, m), 7.13-7.27(2H, m), 7.31(1H, d, J=7.8 Hz), 7.41(2H, d, J=8.7 Hz), 7.71(1H, dt, J=1.7 Hz,7.6 Hz), 8.49-8.55(1H, m), 9.91(1H, s)

(+)ESI-MS: 401$(M+H)^+$, 423$(M+Na)^+$

Example 39

4-Methyl-2-(1-piperidinyl)-N-(4-{[2-(2-pyridinyl)ethyl]amino}phenyl)benzamide

The title compound was obtained according to a similar manner to that of Example 38 from tert-butyl 4-aminophenyl[2-(2-pyridinyl)ethyl]carbamate and 4-methyl-2-(1-

piperidinyl)benzoic acid.

$^1$H-NMR(DMSO-$d_6$):δ 1.47-1.80(6H, m), 2.34(3H, s), 2.85-3.07(6H, m), 3.31-3.44(2H, m), 5.59(1H, t, J=5.7 Hz), 6.61(2H, d, J=8.8 Hz), 7.04(1H, d, J=8.0 Hz), 7.14-7.28(2H, m), 7.33(1H, d, J=7.8 Hz), 7.49(2H, d, J=8.8 Hz), 7.71(1H, dt, J=1.8 Hz, 7.6 Hz), 7.84(1H, d, J=8.0 Hz), 8.49-8.56(1H, m), 11.77(1H, s)

(+)ESI-MS: 415$(M+H)^+$, 437$(M+Na)^+$

Example 40

2-(Hexahydro-1H-azepin-1-yl)-4-methyl-N-(4-{[2-(2-pyridinyl)ethyl]amino}phenyl)benzamide

The title compound was obtained according to a similar manner to that of Example 38 from tert-butyl 4-aminophenyl[2-(2-pyridinyl)ethyl]carbamate and 2-(hexahydro-1H-azepin-1-yl)-4-methylbenzoic acid.

$^1$H-NMR(DMSO-$d_6$):δ 1.52-1.67(4H, m), 1.67-1.85(4H, m), 2.31(3H, s), 2.98(2H, t, J=7.2 Hz), 3.12-3.27(4H, m), 3.29-3.44(2H, m), 5.56(1H, t, J=5.7 Hz), 6.59(2H, d, J=8.8 Hz), 6.86(1H, d, J=7.7 Hz), 7.03(1H, s), 7.17-7.28(1H, m), 7.32(1H, d, J=7.7 Hz), 7.42(2H, d, J=8.8 Hz), 7.58(1H, d, J=7.7 Hz), 7.65-7.77(1H, m), 8.48-8.56(1H, m), 11.19(1H, s)

(+)ESI-MS: 429$(M+H)^+$, 451$(M+Na)^+$

Example 41

4-Methyl-2-(4-methyl-1-piperidinyl)-N-(4-{[2-(2-pyridinyl)ethyl]amino}phenyl)benzamide

The title compound was obtained according to a similar manner to that of Example 38 from tert-butyl 4-aminophenyl[2-(2-pyridinyl)ethyl]carbamate and 4-methyl-2-(4-methyl-1-piperidinyl)benzoic acid.

$^1$H-NMR(DMSO-$d_6$):δ 0.97(3H, d, J=6.4 Hz), 1.29-1.41(2H, m), 1.47-1.59(1H, m), 1.71-1.79(2H, m), 2.34(3H, s), 2.73-2.82(2H, m), 2.99(2H, t, J=7.3 Hz), 3.06-3.12(2H, m), 3.32-3.42(2H, m), 5.58(1H, t, J=5.7 Hz), 6.61(2H, d, J=8.8 Hz), 7.03(1H, d, J=7.9 Hz), 7.16(1H, s), 7.20-7.26(1H, m), 7.33(1H, d, J=7.9 Hz), 7.48(2H, d, J=8.8 Hz), 7.68-7.74(1H, m), 7.83(1H, d, J=7.9 Hz), 8.50-8.55(1H, m), 11.70(1H, s)

(+)ESI-MS: 429$(M+H)^+$, 451$(M+Na)^+$

Example 42

2-(Dimethylamino)-4-methyl-N-(4-{[2-(2-

pyridinyl)ethyl]amino}phenyl)benzamide

The title compound was obtained according to a similar manner to that of Example 38 from tert-butyl 4-aminophenyl[2-(2-pyridinyl)ethyl]carbamate and 2-(dimethylamino)-4-methylbenzoic acid.

$^1$H-NMR(DMSO-$d_6$):δ 2.33(3H, s), 2.75(6H, s), 2.99(2H, t, J=7.2 Hz), 3.30-3.44(2H, m), 5.56(1H, t, J=5.7 Hz), 6.59(2H, d, J=8.8 Hz), 6.94(1H, d, J=8.0 Hz), 7.08(1H, s), 7.18-7.27(1H, m), 7.32(1H, d, J=7.8 Hz), 7.43(2H, d, J=8.8 Hz), 7.64-7.77(2H, m), 8.49-8.55(1H, m), 11.18(1H, s)

(+)ESI-MS: 375$(M+H)^+$, 397$(M+Na)^+$

Preparation 52

A mixture of 2-chloro-6-methylnicotinic acid (3.43 g), tert-butyl 4-aminophenyl[2-(2-pyridinyl)ethyl]carbamate (5.15 g), 1-hydroxybenzotriazole hydrate (3.21 g) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (3.26 g) in N,N-dimethylformamide (30 ml) was stirred at ambient temperature overnight. The reaction mixture was poured into a mixture of ethyl acetate and water and the organic layer was washed with brine and dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was chromatographed on silica gel eluting with ethyl acetate and n-hexane (5:5 v/v). The fractions containing the desired product were collected and evaporated in vacuo to give tert-butyl 4-{[(2-chloro-6-methyl-3-pyridinyl)carbonyl]amino}phenyl[2-(2-pyridinyl)ethyl]carbamate (8.43 g).

$^1$H-NMR(DMSO-$d_6$):δ 1.18(9H, s), 2.35(3H, s), 2.27(2H, t, J=7.3 Hz), 3.79(2H, t, J=7.3 Hz), 7.03-7.11(4H, m), 7.26(1H, d, J=7.8 Hz), 7.50-7.58(3H, m), 7.81(1H, d, J=7.6 Hz), 8.31-8.33(1H, m), 10.47(1H, s)

Example 43

A mixture of tert-butyl 4-{[(2-chloro-6-methyl-3-pyridinyl)carbonyl]amino}phenyl[2-(2-pyridinyl)ethyl]carbamate (700 mg) and piperidine (0.5 ml) in tetrahydrofuran (10 ml) was refluxed under stirring for 5 hours. The reaction mixture was poured into a mixture of ethyl acetate and water and the organic layer was washed with brine and dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue

was chromatographed on silica gel eluting with ethyl acetate and n-hexane (5:5 v/v). The fractions containing the desired product were collected and evaporated in vacuo to give tert-butyl 4-({[6-methyl-2-(1-piperidinyl)-3-pyridinyl]carbonyl}amino)phenyl[2-(2-pyridinyl)ethyl]carbamate (520 mg).

$^1$H-NMR(DMSO-$d_6$):δ 1.32(9H, s), 1.55-1.57(6H, m), 2.40(3H, s), 2.91(2H, t, J=7.4 Hz), 3.22-3.33(4H, m), 3.91(2H, t, J=7.4 Hz), 6.84(1H, d, J=7.6 Hz), 7.16-7.25(4H, m), 7.64-7.71(3H, m), 7.77(1H, d, J=7.6 Hz), 8.45-8.46(1H, m), 10.62(1H, s)

Example 44

A mixture of tert-butyl 4-({[6-methyl-2-(1-piperidinyl)-3-pyridinyl]carbonyl}amino)phenyl[2-(2-pyridinyl)ethyl]carbamate (520 mg) and trifluoroacetic acid (1.0 ml) in dichloromethane (5 ml) was stirred at ambient temperature for 5 hours. The reaction mixture was evaporated in vacuo. The residue was dissolved in a mixture of ethyl acetate and water, and the mixture was adjusted to pH 8.5 with aqueous potassium carbonate solution. The organic layer was washed with brine and dried over magnesium sulfate. The solvent was concentrated in vacuo and the precipitate was collected by filtration to give 6-methyl-2-(1-piperidinyl)-N-(4-{[2-(2-pyridinyl)ethyl]amino}phenyl)nicotinamide (398 mg).

$^1$H-NMR(DMSO-$d_6$):δ 1.52-1.58(6H, m), 2.39(3H, s), 2.99(2H, t, J=7.4 Hz), 3.18-3.21(4H, m), 3.34-3.39(2H, m), 5.55-5.58(1H, m), 6.59(2H, d, J=8.8 Hz), 6.84 (1H, d, J=7.6 Hz), 7.21-7.24(1H, m), 7.32(1H, d, J=7.8 Hz), 7.45(2H, d, J=8.8 Hz), 7.69-7.73(1H, m), 7.77(1H, d, J=7.6 Hz), 8.51-8.52(1H, m), 10.33 (1H, s)

(+)ESI-MS(m/z): 416$(M+H)^+$, 438$(M+Na)^+$

Example 45

tert-Butyl 4-({[6-methyl-2-(4-methyl-1-piperidinyl)-3-pyridinyl]carbonyl}amino)phenyl[2-(2-pyridinyl)ethyl]carbamate

The title compound was obtained according to a similar manner to that of Example 43 from tert-butyl 4-{[(2-chloro-6-methyl-3-pyridinyl)carbonyl]amino}phenyl[2-(2-pyridinyl)ethyl]carbamate and 4-methylpiperidine.

$^1$H-NMR(DMSO-$d_6$):δ 0.89(3H, d, J=6.1 Hz), 1.14-1.46(2H, m),

1.47(9H, s), 1.50-1.52(1H, m), 1.60-1.66(2H, m), 2.40(3H, s), 2.76-2.95(4H, m), 3.64-3.70(2H, m), 3.88-3.97(2H, m), 6.82(1H, d, J=7.7 Hz), 7.15-7.26(4H, m), 7.65-7.78(4H, m), 8.44-8.47(1H, m), 10.57(1H, s)

Example 46

6-Methyl-2-(4-methyl-1-piperidinyl)-N-(4-{[2-(2-pyridinyl)ethyl]amino}phenyl)nicotinamide

The title compound was obtained according to a similar manner to that of Example 44 from tert-butyl 4-({[6-methyl-2-(4-methyl-1-piperidinyl)-3-pyridinyl]carbonyl}amino)phenyl[2-(2-pyridinyl)ethyl]carbamate.

$^1$H-NMR(DMSO-$d_6$):δ 0.90(6H, d, J=6.5 Hz), 1.17-1.26(2H, m), 1.49-1.51(1H, m), 1.62-1.65(2H, m), 2.39(3H, s), 2.99(2H, t, J=7.4 Hz), 3.34-3.39(2H, m), 3.61-3.65(2H, m), 5.56-5.59(1H, m), 6.58(2H, d, J=8.9 Hz), 6.82(1H, d, J=7.6 Hz), 7.21-7.24(1H, m), 7.32(1H, d, J=7.8 Hz), 7.45(2H, d, J=8.9 Hz), 7.69-7.76(2H, m), 8.51-8.52(1H, m), 10.26(1H, s)

(+)ESI-MS(m/z): 430$(M+H)^+$, 452$(M+Na)^+$

Example 47

tert-Butyl 4-({[6-methyl-2-(4-thiomorpholinyl)-3-pyridinyl]carbonyl}amino)phenyl[2-(2-pyridinyl)ethyl]carbamate

The title compound was obtained according to a similar manner to that of Example 43 from tert-butyl 4-{[(2-chloro-6-methyl-3-pyridinyl)carbonyl]amino}phenyl[2-(2-pyridinyl)ethyl]carbamate and thiomorpholine.

$^1$H-NMR(DMSO-$d_6$):δ 1.32(9H, s), 2.41(3H, s), 2.63-2.68(4H, m), 2.91(2H, t, J=7.4 Hz), 3.52-3.57(4H, m), 3.91(2H, t, J=7.4 Hz), 6.85(1H, d, J=7.7 Hz), 7.15-7.26(4H, m), 7.65-7.75(4H, m), 8.44-8.47(1H, m), 10.42(1H, s)

Example 48

6-Methyl-N-(4-{[2-(2-pyridinyl)ethyl]amino}phenyl)-2-(4-thiomorpholinyl)nicotinamide

The title compound was obtained according to a similar manner to that of Example 44 from tert-butyl 4-({[6-methyl-2-(4-thiomorpholinyl)-3-pyridinyl]carbonyl}amino)phenyl[2-(2-pyridinyl)ethyl]carbamate.

$^1$H-NMR(DMSO-$d_6$):δ 2.39(3H, s), 2.63-2.68(4H, m), 2.98(2H, t, J=7.4 Hz), 3.33-3.40(2H, m), 3.50-3.55(4H, m), 5.60(1H, s),

6.59(2H, d, J=8.8 Hz), 6.86 (1H, d, J=7.6 Hz), 7.19-7.26(1H, m), 7.32(1H, d, J=7.6 Hz), 7.44(2H, d, J=8.8 Hz), 7.67-7.75(2H, m), 8.50-8.53(1H, m), 10.05(1H, s)
(+)ESI-MS(m/z): 434$(M+H)^+$, 456$(M+Na)^+$

Example 49

tert-Butyl 4-({[6-methyl-2-(4-morpholinyl)-3-pyridinyl]carbonyl}amino)phenyl[2-(2-pyridinyl)ethyl]carbamate

The title compound was obtained according to a similar manner to that of Example 43 from tert-butyl 4-{[(2-chloro-6-methyl-3-pyridinyl)carbonyl]amino}phenyl[2-(2-pyridinyl)ethyl]carbamate and morpholine.
$^1$H-NMR(DMSO-$d_6$):δ 1.29(9H, s), 2.48(3H, s), 2.91(2H, t, J=7.4 Hz), 3.23-3.28(4H, m), 3.63-3.67(4H, m), 3.96(2H, t, J=7.4 Hz), 6.86(1H, d, J=7.7Hz), 7.15-7.26(4H, m), 7.65-7.77(4H, m), 8.45-8.47(1H, m), 10.49(1H, s)

Example 50

6-Methyl-N-(4-{[2-(2-pyridinyl)ethyl]amino}phenyl)-2-(4-morpholinyl)nicotinamide

The title compound was obtained according to a similar manner to that of Example 44 from tert-butyl 4-{[(2-chloro-6-methyl-3-pyridinyl)carbonyl]amino}phenyl[2-(2-pyridinyl)ethyl]carbamate.
$^1$H-NMR(DMSO-$d_6$):δ 2.40(3H, s), 2.98(2H, t, J=7.4 Hz), 3.21-3.26(4H, m), 3.33-3.40(4H, m), 3.66-3.68(2H, m), 5.58(1H, br.s), 6.58(2H, d, J=8.9 Hz), 6.85(1H, d, J=7.7 Hz), 7.19-7.26(1H, m), 7.32(1H, d, J=7.7 Hz), 7.45(2H, d, J=8.9 Hz), 7.67-7.75(2H, m), 8.50-8.53(1H, m), 10.11(1H, s)
(+)ESI-MS(m/z): 418$(M+H)^+$, 440$(M+Na)^+$

Preparation 53

tert-Butyl 4-{[(2-chloro-3-pyridinyl)carbonyl]amino}-phenyl[2-(2-pyridinyl)ethyl]carbamate

The title compound was obtained according to a similar manner to that of Preparation 52 from 2-chloronicotinic acid and tert-butyl 4-aminophenyl[2-(2-pyridinyl)ethyl]carbamate.
$^1$H-NMR(DMSO-$d_6$):δ 1.29(9H, s), 2.90(2H, t, J=7.4 Hz), 3.92(2H, t, J=7.4 Hz), 7.20-7.26(4H, m), 7.56-7.59(1H, m), 7.66-7.70(3H, m), 8.08-8.10(1H, m), 8.54-8.55(1H, m), 10.69(1H, s)

Example 51

tert-Butyl 4-({[2-(1-piperidinyl)-3-pyridinyl]carbonyl}amino)phenyl[2-(2-pyridinyl)ethyl]carbamate

The title compound was obtained according to a similar manner to that of Example 43 from tert-butyl 4-{[(2-chloro-6-methyl-3-pyridinyl)carbonyl]amino}phenyl[2-(2-pyridinyl)ethyl]carbamate and piperidine.

$^1$H-NMR(DMSO-$d_6$):δ 1.32(9H, s), 1.55(6H, s), 2.91(2H, t, J=7.4 Hz), 3.26(4H, s), 3.91(2H, t, J=7.4 Hz), 6.95(1H, dd, J=4.7 Hz,7.4 Hz), 7.16-7.27(4H, m), 7.66-7.72(3H, m), 7.81-7.85(1H, m), 8.28-8.31(1H, m), 8.46(1H, d, J=4.1 Hz), 10.57(1H, s)

Example 52

2-(1-Piperidinyl)-N-(4-{[2-(2-pyridinyl)ethyl]amino}phenyl)nicotinamide

The title compound was obtained according to a similar manner to that of Example 44 from tert-butyl 4-({[2-(1-piperidinyl)-3-pyridinyl]carbonyl}amino)phenyl[2-(2-pyridinyl)ethyl]carbamate.

$^1$H-NMR(DMSO-$d_6$):δ 1.52-1.58(6H, m), 2.39(3H, s), 2.99(2H, t, J=7.4 Hz), 3.18-3.21(4H, m), 3.34-3.39(2H, m), 5.55-5.58(1H, m), 6.59(2H, d, J=8.8 Hz), 6.84(1H, d, J=7.6 Hz), 7.21-7.24(1H, m), 7.32(1H, d, J=7.8 Hz), 7.45(2H, d, J=8.8 Hz), 7.69-7.73(1H, m), 7.77(1H, d, J=7.6Hz), 8.51-8.52(1H, m), 10.33(1H, s)

(+)ESI-MS(m/z): 402$(M+H)^+$, 424$(M+Na)^+$

Example 53

tert-Butyl 4-({[2-(4-methyl-1-piperidinyl)-3-pyridinyl]carbonyl}amino)phenyl[2-(2-pyridinyl)ethyl]carbamate

The title compound was obtained according to a similar manner to that of Example 43 from tert-butyl 4-{[(2-chloro-6-methyl-3-pyridinyl)carbonyl]amino}phenyl[2-(2-pyridinyl)ethyl]carbamate and 4-methylpiperidine.

$^1$H-NMR(DMSO-$d_6$):δ 0.89(3H, d, J=6.1 Hz), 1.21(9H, s), 1.14-1.18(2H, m), 1.21-1.32(3H, m), 2.78-2.95(4H, m), 3.69-3.75(2H, m), 3.92(2H, t, J=7.4Hz), 6.93-6.97(1H, m), 7.16-7.26(4H, m), 7.65-7.70(3H, m), 7.71-7.84(1H, m), 8.27-8.31(1H, m), 8.45-8.47(1H, m), 10.54(1H, s)

Example 54

2-(4-Methyl-1-piperidinyl)-N-(4-{[2-(2-pyridinyl)ethyl]amino}phenyl)nicotinamide

The title compound was obtained according to a similar manner to that of Example 44 from tert-butyl 4-({[2-(4-methyl-1-piperidinyl)-3-pyridinyl]carbonyl}amino)phenyl[2-(2-pyridinyl)ethyl]carbamate.

$^1$H-NMR(DMSO-$d_6$):δ 0.87(3H, d, J=6.2 Hz), 1.05-1.30(2H, m), 1.35-1.66(3H, m), 2.76-2.87(2H, m), 2.99(2H, t, J=7.3 Hz), 3.33-3.41(2H, m), 3.66-3.72(2H, m), 5.63(1H, br.s), 6.59(2H, d J=8.8 Hz), 6.90-6.96(1H, m), 7.23-7.26(1H, m), 7.33(1H, d, J=7.7 Hz), 7.44(2H, d, J=8.8 Hz), 7.68-7.83(2H, m), 8.25-8.28(1H, m), 8.50-8.53(1H, m), 10.21(1H, s)

(+)ESI-MS(m/z): 416$(M+H)^+$, 438$(M+Na)^+$

Example 55

A mixture of tert-butyl 4-{[(2-chloro-6-methyl-3-pyridinyl)carbonyl]amino}phenyl[2-(2-pyridinyl)ethyl]carbamate (700 mg) in 2M dimethylamine-tetrahydrofuran solution (10 ml) was stirred at 65-70°C for 10 hours. The reaction mixture was poured into a mixture of ethyl acetate and water and the organic layer was washed with brine and dried over magnesium sulfate. The solvent was concentrated in vacuo and the precipitate was collected by filtration to give tert-butyl 4-({[2-(dimethylamino)-6-methyl-3-pyridinyl]carbonyl}amino)-phenyl[2-(2-pyridinyl)ethyl]carbamate (460 mg).

$^1$H-NMR(DMSO-$d_6$):δ 1.33(9H, s), 2.37(3H, s), 2.90(2H, t, J=7.4 Hz), 2.96(6H, s), 3.91(2H, t, J=7.4 Hz), 6.62(1H, d, J=7.6 Hz), 7.15-7.25(4H, m), 7.60(1H, d, J=7.6 Hz), 7.66-7.69(3H, m), 8.46-8.47(1H, m), 10.35(1H, s)

Example 56

2-(Dimethylamino)-6-methyl-N-(4-{[2-(2-pyridinyl)ethyl]amino}phenyl)nicotinamide

The title compound was obtained according to a similar manner to that of Example 44 from tert-butyl 4-({[2-(dimethylamino)-6-methyl-3-pyridinyl]carbonyl}amino)phenyl[2-(2-pyridinyl)ethyl]carbamate.

$^1$H-NMR(DMSO-$d_6$):δ 2.35(3H, s), 2.94(6H, s), 3.00(2H, t, J=7.40 Hz), 3.35-3.39(2H, m), 6.57-6.61(3H, m), 7.24-7.34(1H, m), 7.35(1H, d, J=7.8 Hz), 7.41(2H, d, J=8.8 Hz), 7.55 (1H, d, J=7.5 Hz), 7.72-7.76(1H, m), 8.52-8.54(1H, m), 9.94(1H, s)

(+)ESI-MS(m/z): 376$(M+H)^+$, 398$(M+Na)^+$

Example 57

tert-Butyl 4-({[2-(dimethylamino)-3-pyridinyl]carbonyl}amino)phenyl[2-(2-pyridinyl)ethyl]carbamate

The title compound was obtained according to a similar manner to that of Example 55 from tert-butyl 4-{[(2-chloro-3-pyridinyl)carbonyl]amino}phenyl[2-(2-pyridinyl)ethyl]carbamate and dimethylamine.

$^1$H-NMR(DMSO-$d_6$):δ 1.33(9H, s), 2.90(2H, t, J=7.4 Hz), 2.97(6H, s), 3.91(2H, t, J=7.4 Hz), 6.72-6.78(1H, m), 7.15-7.26(4H, m), 7.65-7.74(4H, m), 8.19-8.22(1H, m), 8.45-8.48(1H, m), 10.42(1H, s)

Example 58

2-(Dimethylamino)-N-(4-{[2-(2-pyridinyl)ethyl]amino}-phenyl)nicotinamide

The title compound was obtained according to a similar manner to that of Example 44 from tert-butyl 4-({[2-(dimethylamino)-3-pyridinyl]carbonyl}amino)phenyl[2-(2-pyridinyl)ethyl]carbamate.

$^1$H-NMR(DMSO-$d_6$):δ 2.98(2H, t, J=7.4 Hz), 2.96(6H, s), 3.34-3.40(2H, m), 6.57(2H, d, J=8.8 Hz), 6.70-6.76(1H, m), 7.23-7.33(2H, m), 7.41(2H, d, J=8.8 Hz), 7.60-7.71(2H, m), 8.16-8.18(1H, m), 8.52(1H, d, J=4.0 Hz), 9.99(1H, s)

(+)ESI-MS(m/z): 362$(M+H)^+$, 384$(M+Na)^+$

Preparation 54

2-Chloro-6-methyl-N-(4-{[2-(2-pyridinyl)ethyl]amino}-phenyl)nicotinamide

The title compound was obtained according to a similar manner to that of Example 44 from tert-butyl 4-{[(2-chloro-6-methyl-3-pyridinyl)carbonyl]amino}phenyl[2-(2-pyridinyl)ethyl]carbamate.

$^1$H-NMR(DMSO-$d_6$):δ 2.49(3H, s), 2.98(2H, t, J=7.4 Hz), 3.33-3.42(2H, m), 5.62(1H, t, J=5.7 Hz), 6.58(2H, d, J=8.9 Hz), 7.20-7.43(5H, m), 7.67-7.71(1H, m), 7.89(1H, d, J=7.7 Hz), 8.50-8.53(1H, m), 10.14(1H, s)

(+)ESI-MS(m/z): 367$(M+H)^+$, 389$(M+Na)^+$

Preparation 55

A mixture of 2-chloro-6-methylnicotinic acid (2.06 g), 4-[2-(2-pyridinyl)ethoxy]phenylamine (2.70 g), 1-

hydroxybenzotriazole hydrate (1.93 g) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (1.96 g) in N,N-dimethylformamide (30 ml) was stirred at ambient temperature overnight. The reaction mixture was poured into a mixture of ethyl acetate and water and the organic layer was washed with brine and dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was chromatographed on silica gel eluting with ethyl acetate and n-hexane (7:3-9:1 v/v). The fractions containing the desired product were collected and evaporated in vacuo to give 2-chloro-6-methyl-N-{4-[2-(2-pyridinyl)ethoxy]phenyl}nicotinamide (2.95 g).

$^1$H-NMR(DMSO-$d_6$):δ 2.49(3H, s), 3.19(2H, t, J=6.6 Hz), 4.34(2H, t, J=6.6 Hz), 6.92-6.94(2H, m), 7.24-7.25(1H, m), 7.37-7.42(2H, m), 7.58-7.60(2H, m), 7.72-7.74(1H, m), 7.93(1H, d, J=7.7 Hz), 8.52-8.53(1H, m), 10.41(1H, s)

(+)ESI-MS(m/z): 368$(M+H)^+$, 390$(M+Na)^+$

Example 59

A mixture of 2-chloro-6-methyl-N-{4-[2-(2-pyridinyl)ethoxy]phenyl}nicotinamide (440 mg) and piperidine (0.5 ml) in tetrahydrofuran (10 ml) was refluxed under stirring for 5 hours. The reaction mixture was poured into a mixture of ethyl acetate and water and the organic layer was washed with brine and dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was chromatographed on silica gel eluting with ethyl acetate and n-hexane (7:3 v/v). The fractions containing the desired product were collected and concentrated in vacuo and the precipitate was collected by filtration to give 6-methyl-2-(1-piperidinyl)-N-{4-[2-(2-pyridinyl)ethoxy]phenyl}nicotinamide (425 mg).

$^1$H-NMR(DMSO-$d_6$):δ 1.53(6H, br.s), 2.39(3H, s), 3.18(2H, t, J=6.6 Hz), 4.33(2H, t, J=6.6 Hz), 6.82(1H, d, J=7.6 Hz), 6.92(2H, d, J=9.0 Hz), 7.21-7.28(1H, m), 7.37(1H, d, J=7.8 Hz), 7.62(2H, d, J=9.0 Hz), 7.69-7.77(2H, m), 8.50-8.53(1H, m), 10.44(1H, s)

(+)ESI-MS(m/z): 417$(M+H)^+$, 439$(M+Na)^+$

Example 60

6-Methyl-2-(4-methyl-1-piperidinyl)-N-{4-[2-(2-

pyridinyl)ethoxy]phenyl}nicotinamide

The title compound was obtained according to a similar manner to that of Example 44 from 2-chloro-6-methyl-N-{4-[2-(2-pyridinyl)ethoxy]phenyl}nicotinamide and 4-methylpiperidine.

$^1$H-NMR(DMSO-$d_6$):δ 0.88(3H, d, J=6.2 Hz), 1.14-1.25(2H, m), 1.28-1.61(3H, m), 2.39 (3H, s), 2.52-2.86(2H, m), 3.18 (2H, t, J=6.6 Hz), 3.62-3.68(2H, m), 4.33(2H, t, J=6.6 Hz), 6.81(1H, d, J=7.6 Hz), 6.92(2H, d, J=9.0 Hz), 7.23-7.28(1H, m), 7.37(1H, d, J=7.7Hz), 7.62(2H, d, J=9.0 Hz), 7.69-7.77(2H, m), 8.50-8.53(1H, m), 10.40(1H, s)

(+)ESI-MS(m/z): 431$(M+H)^+$, 453$(M+Na)^+$

Example 61

A mixture of 2-chloro-6-methyl-N-{4-[2-(2-pyridinyl)ethoxy]phenyl}nicotinamide (736 mg) in 2M dimethylamine-tetrahydrofuran solution (10 ml) was stirred at 65-70°C for 10 hours. The reaction mixture was poured into a mixture of ethyl acetate and water and the organic layer was washed with brine and dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was chromatographed on silica gel eluting with ethyl acetate and n-hexane (7:3 v/v). The fractions containing the desired product were collected and concentrated in vacuo and the precipitate was collected by filtration to give 2-(dimethylamino)-6-methyl-N-{4-[2-(2-pyridinyl)ethoxy]phenyl}-nicotinamide (205 mg).

$^1$H-NMR(DMSO-$d_6$):δ 2.35(3H, s), 3.14(6H, s), 3.29(2H, t, J=6.7 Hz), 4.33(2H, t, J=6.7 Hz), 6.61(1H, d, J=7.5 Hz), 6.90(2H, d, J=9.0 Hz), 7.21-7.28(1H, dm), 7.36(1H, d, J=7.7 Hz), 7.54-7.60(3H, m), 7.69-7.77(1H, m), 8.50-8.52(1H, m), 10.14(1H, s)

(+)ESI-MS(m/z): 377$(M+H)^+$, 399$(M+Na)^+$

Preparation 56

2-Chloro-N-{4-[2-(2-pyridinyl)ethoxy]phenyl}nicotinamide

The title compound was obtained according to a similar manner to that of Preparation 55 from 2-chloronicotinic acid and 4-[2-(2-pyridinyl)ethoxy]phenylamine.

$^1$H-NMR(DMSO-$d_6$):δ 3.19(2H, t, J=6.6 Hz), 4.34(2H, t, J=6.6 Hz), 6.94(2H, d, J=9.0 Hz), 7.25-7.28(1H, m), 7.39(1H, d, J=7.8 Hz),

7.54-7.61(3H, m), 7.74-7.76(1H, m), 8.04-8.07(1H, m), 8.51-8.53(2H, m), 10.49(1H, s)
(+)ESI-MS(m/z): 354$(M+H)^+$, 376$(M+Na)^+$

Example 62

2-(1-Piperidinyl)-N-{4-[2-(2-pyridinyl)ethoxy]phenyl}-nicotinamide

The title compound was obtained according to a similar manner to that of Example 59 from N-{4-[2-(2-pyridinyl)ethoxy]phenyl}nicotinamide and piperidine.
$^1$H-NMR(DMSO-$d_6$):δ 1.53(6H, br.s), 3.15-3.24(6H, m), 4.34(2H, t, J=6.6 Hz), 6.90-6.97(3H, m), 7.37(1H, d, J=7.7Hz), 7.63(2H, d, J=9.0 Hz), 7.69-7.83(2H, m), 8.16-8.29(1H, m), 8.51-8.53(1H, m), 10.40(1H, s)
(+)ESI-MS(m/z): 403$(M+H)^+$, 425$(M+Na)^+$

Example 63

2-(4-Methyl-1-piperidinyl)-N-{4-[2-(2-pyridinyl)ethoxy]-phenyl}nicotinamide

The title compound was obtained according to a similar manner to that of Example 59 from N-{4-[2-(2-pyridinyl)ethoxy]phenyl}nicotinamide and 4-methylpiperidine.
$^1$H-NMR(DMSO-$d_6$):δ 0.88(3H, d, J=6.1 Hz), 1.02-1.27(2H, m), 1.30-1.64(3H, m), 2.76-2.88(2H, m), 3.19(2H, t, J=6.6 Hz), 3.68-3.74(2H, m), 4.34(2H, t, J=6.6 Hz), 6.90-6.95(3H, m), 7.24-7.25(1H, m), 7.37(1H, d, J=7.7 Hz), 7.62-7.83(4H, m), 8.26-8.29(1H, m), 8.51-8.53(1H, m), 10.39(1H, s)
(+)ESI-MS(m/z): 417$(M+H)^+$, 439$(M+Na)^+$

Preparation 57

2-Chloro-5-nitropyridine (4.76 g) was added portionwise to a solution of 2-hydroxyethylpyridine (4.43 g) and potassium tert-butoxide (4.04 g) in tetrahydrofuran (60 ml). The mixture was stirred at a temperature between 5 to 20°C under ice-cooling and the resultant mixture was stirred at ambient temperature for 3 hours. The reaction mixture was poured into a mixture of ethyl acetate and water. The organic layer was washed with 5% aqueous potassium carbonate solution and brine and dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was chromatographed on silica gel eluting with ethyl acetate:n-hexane (5:5 v/v). The fractions

containing the desired product were collected and concentrated in vacuo and the precipitate was collected by filtration to give 5-nitro-2-[2-(2-pyridinyl)ethoxy]pyridine (2.42 g).
$^1$H-NMR(DMSO-$d_6$):δ 3.24(2H, t, J=6.68 Hz), 4.80(2H, t, J=6.68 Hz), 6.98(1H, d, J=9.16 Hz), 7.24-7.28(1H, m), 7.35(1H, d, J=7.78 Hz), 7.69-7.77(1H, m), 8.42-8.52(2H, m), 9.09(1H, d, J=2.86 Hz)

Preparation 58

A mixture of 5-nitro-2-[2-(2-pyridinyl)ethoxy]pyridine (736 mg), iron powder (900 mg) and ammonium chloride (101 mg) in ethanol (40 ml) and water (8 ml) was refluxed under stirring for 2.5 hours. After removal of the insoluble materials by filtration, the solvent was evaporated in vacuo and the residue was dissolved in ethyl acetate and water. The organic layer was washed with brine and dried over magnesium sulfate. The solvent was evaporated in vacuo to give 6-[2-(2-pyridinyl)ethoxy]-3-pyridinamine (664 mg).

Preparation 59

2-Chloro-6-methyl-N-{6-[2-(2-pyridinyl)ethoxy]-3-pyridinyl}nicotinamide

The title compound was obtained according to a similar manner to that of Preparation 55 from 2-chloro-6-methylnicotinic acid and 6-[2-(2-pyridinyl)ethoxy]-3-pyridinamine.
$^1$H-NMR(DMSO-$d_6$):δ 2.50(3H, s), 3.19(2H, t, J=6.8 Hz), 4.34(2H, t, J=6.8Hz), 6.80(1H, d, J=8.9 Hz), 7.23-7.43(3H, m), 7.68-7.73(1H, m), 7.95-8.01(2H, m), 8.45-8.53(2H, m), 10.61(1H, s)

Example 64

6-Methyl-2-(4-methyl-1-piperidinyl)-N-{6-[2-(2-pyridinyl)ethoxy]-3-pyridinyl}nicotinamide

The title compound was obtained according to a similar manner to that of Example 59 from 2-chloro-6-methyl-N-{6-[2-(2-pyridinyl)ethoxy]-3-pyridinyl}nicotinamide and 4-methylpiperidine.
$^1$H-NMR(DMSO-$d_6$):δ 0.89(3H, d, J=6.2 Hz), 1.06-1.30(2H, m), 1.32-1.72(3H, m), 2.39(3H, s), 2.72-2.90(2H, m), 3.18(2H, t, J=6.7 Hz), 3.65-3.70(2H, m), 4.60(2H, t, J=6.7 Hz), 6.76-6.81(2H, m), 7.32-7.36(2H, m), 7.71-7.75(2H, m), 7.97-8.03(1H,

m), 8.47-8.51(2H, m), 10.46(1H, s)
(+)ESI-MS(m/z): 432$(M+H)^+$, 454 $(M+Na)^+$

Example 65

2-(Dimethylamino)-6-methyl-N-{6-[2-(2-pyridinyl)ethoxy]-3-pyridinyl}nicotinamide

The title compound was obtained according to a similar manner to that of Example 61 from 2-chloro-6-methyl-N-{6-[2-(2-pyridinyl)ethoxy]-3-pyridinyl}nicotinamide and dimethylamine.

$^1$H-NMR(DMSO-$d_6$):δ 2.36(3H, s), 2.95(6H, s), 3.18(2H, t, J=6.7 Hz), 4.61(2H, t, J=6.7 Hz), 6.62(1H, d, J=7.5 Hz), 6.77(1H, d, J=8.9 Hz), 7.20-7.26(1H, m), 7.34(1H, d, J=7.8 Hz), 7.68-7.76(1H, m), 7.95-8.00(1H, m), 8.46-8.52(2H, m), 10.30(1H, s)
(+)ESI-MS(m/z): 378$(M+H)^+$, 400$(M+Na)^+$

Preparation 60

A mixture of 2-chloro-6-methylnicotinic acid (772 mg), 3-{[4-(4-aminophenyl)-1-piperazinyl]methyl}benzonitrile (1.38 g), 1-hydroxybenzotriazole hydrate (723 mg) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (733 mg) in N,N-dimethylformamide (15 ml) was stirred at ambient temperature overnight. The reaction mixture was poured into a mixture of ethyl acetate and water and the organic layer was washed with brine and dried over magnesium sulfate. The solvent was concentrated in vacuo and the precipitate was collected by filtration to give 2-chloro-N-{4-[4-(3-cyanobenzyl)-1-piperazinyl]phenyl}-6-methylnicotinamide (1.69 g).
$^1$H-NMR(DMSO-$d_6$):δ 2.51(3H, s), 2.51-2.54(4H, m), 3.09-3.11(4H, m), 3.60(2H, s), 6.92(2H, d, J=9.0 Hz), 7.38(1H, d, J=7.8 Hz), 7.60-7.68(3H, m), 7.72-7.76(3H, m), 7.91(1H, d, J=7.7 Hz), 10.31(1H, s)
(+)ESI-MS(m/z): 446$(M+H)^+$, 468$(M+Na)^+$

Example 66

A mixture of 2-chloro-N-{4-[4-(3-cyanobenzyl)-1-piperazinyl]phenyl}-6-methylnicotinamide (400 mg) and 4-methylpiperidine (0.5 ml) in tetrahydrofuran (5 ml) was refluxed under stirring for 12 hours. The reaction mixture was poured into a mixture of ethyl acetate and water and the organic layer was washed with brine and dried over magnesium

sulfate. The solvent was concentrated in vacuo and the precipitate was collected by filtration to give N-{4-[4-(3-cyanobenzyl)-1-piperazinyl]phenyl}-6-methyl-2-(4-methyl-1-piperidinyl)nicotinamide (380 mg).

$^1$H-NMR(DMSO-$d_6$):δ 0.90(3H, d, J=6.2 Hz), 1.17-1.24(2H, m), 1.27-1.69(3H, m), 2.39(3H, s), 2.50-2.52(4H, m), 2.75-2.86(2H, m), 3.09-3.10(4H, m), 3.59(2H, s), 3.59-3.67(2H, m), 6.82(1H, d, J=7.7 Hz), 6.92(2H, d, J=9.0 Hz), 7.53-7.60(3H, m), 7.68-7.77(4H, m), 10.39(1H, s)

(+)ESI-MS(m/z): 509$(M+H)^+$, 531$(M+Na)^+$

Example 67

A mixture of 2-chloro-N-{4-[4-(3-cyanobenzyl)-1-piperazinyl]phenyl}-6-methylnicotinamide (400 mg) in 2M dimethylamine-tetrahydrofuran solution (10 ml) was stirred at 65-70°C for 10 hours. The reaction mixture was poured into a mixture of ethyl acetate and water and the organic layer was washed with brine and dried over magnesium sulfate. The solvent was evaporated in vacuo and the residue was chromatographed on silica gel eluting with ethyl acetate and n-hexane (7:3 v/v). The fractions containing the desired product were collected and concentrated in vacuo and the precipitate was collected by filtration to give N-{4-[4-(3-cyanobenzyl)-1-piperazinyl]phenyl}-2-(dimethylamino)-6-methylnicotinamide (90 mg).

$^1$H-NMR(DMSO-$d_6$):δ 2.35(3H, s), 2.49-2.54(4H, m), 2.94(6H, s), 3.07-3.09(4H, m), 3.59(2H, s), 6.60(1H, d, J=7.5 Hz), 6.89(2H, d, J=9.0 Hz), 7.51-7.60(4H, m), 7.68-7.77(3H, m), 10.07(1H, s)

(+)ESI-MS(m/z): 455$(M+H)^+$, 477$(M+Na)^+$

Preparation 61

2-Chloro-N-{6-[4-(3-cyanobenzyl)-1-piperazinyl]-3-pyridinyl}-6-methylnicotinamide

The title compound was obtained according to a similar manner to that of Preparation 60 from 3-{[4-(5-amino-2-pyridinyl)-1-piperazinyl]methyl}benzonitrile and 2-chloro-6-methylnicotinic acid.

$^1$H-NMR(DMSO-$d_6$):δ 2.45(3H, s), 2.48-2.51(4H, m), 3.43-3.48(4H, m), 3.59(2H, s), 6.85(1H, d, J=9.1 Hz), 7.40(1H, d, J=7.8 Hz), 7.53-7.60(1H, m), 7.69-7.90(5H, m), 8.38(1H, d, J=2.6 Hz),

10.40(1H, s)

(+)ESI-MS(m/z): 447$(M+H)^+$, 469$(M+Na)^+$

Example 68

N-{6-[4-(3-Cyanobenzyl)-1-piperazinyl]-3-pyridinyl}-6-methyl-2-(4-methyl-1-piperidinyl)nicotinamide

The title compound was obtained according to a similar manner to that of Example 66 from 2-chloro-N-{6-[4-(3-cyanobenzyl)-1-piperazinyl]-3-pyridinyl}-6-methylnicotinamide and 4-methylpiperidine.

$^1$H-NMR(DMSO-$d_6$):δ 0.89(3H, d, J=6.2 Hz), 1.14-1.21(2H, m), 1.26-1.66(3H, m), 2.39(3H, s), 2.45-2.51(4H, m), 2.75-2.86(2H, m), 3.43-3.58(4H, m), 3.58-3.69(4H, m), 6.79-6.87(2H, m), 7.53-7.60(1H, m), 7.69-7.78(4H, m), 7.87-7.93(1H, m), 8.42(1H, d, J=2.6 Hz), 10.36(1H, s)

(+)ESI-MS(m/z): 510$(M+H)^+$, 532$(M+Na)^+$

Example 69

N-{6-[4-(3-Cyanobenzyl)-1-piperazinyl]-3-pyridinyl}-2-(dimethylamino)-6-methylnicotinamide

The title compound was obtained according to a similar manner to that of Example 67 from 2-chloro-N-{6-[4-(3-cyanobenzyl)-1-piperazinyl]-3-pyridinyl}-6-methylnicotinamide and dimethylamine.

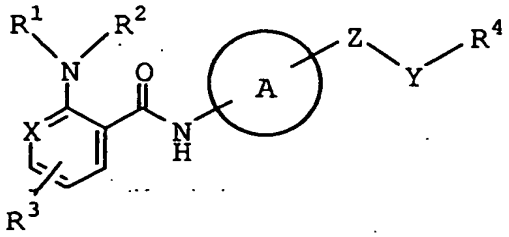
$^1$H-NMR(DMSO-$d_6$):δ 2.35(3H, s), 2.45-2.51(4H, m), 3.34(6H, s), 3.42-3.46(4H, m), 3.58(2H, s), 6.61(1H, d, J=7.6 Hz), 6.83(2H, d, J=9.1 Hz), 7.53-7.60(2H, m), 7.68-7.88(4H, m), 8.39-8.40(1H, m), 10.12(1H, s)

(+)ESI-MS(m/z): 456$(M+H)^+$, 478$(M+Na)^+$

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of the formula (I)



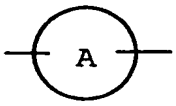
(I)

wherein

$R^1$ and $R^2$ are each independently lower alkyl, or $R^1$, $R^2$ and nitrogen atom to which they are attached form an optionally substituted, saturated or partially saturated N-containing heterocyclic group;

$R^3$ is hydrogen, halogen, lower alkyl, lower alkoxy, halo(lower)alkyl or $-NR^5R^6$ (wherein $R^5$ and $R^6$ are each independently lower alkyl, or $R^5$, $R^6$ and nitrogen atom to which they are attached form an optionally substituted, saturated or partially saturated N-containing heterocyclic group);

$R^4$ is aryl or heteroaryl, each of which is optionally substituted by cyano, amino, lower alkyl or heteroaryl substituted by one or more lower alkyl;



is bivalent residue derived from aryl or heteroaryl;

X is N or C($R^3$) (wherein $R^3$ is as defined above);

Y is $-(A^1)_n-(A^2)_m-$

wherein $A^1$ is -O-, -NH-, $-N(R^7)-$, -CO- or -NH-CO-,

wherein $R^7$ is amino protective group,

$A^2$ is lower alkylene, and

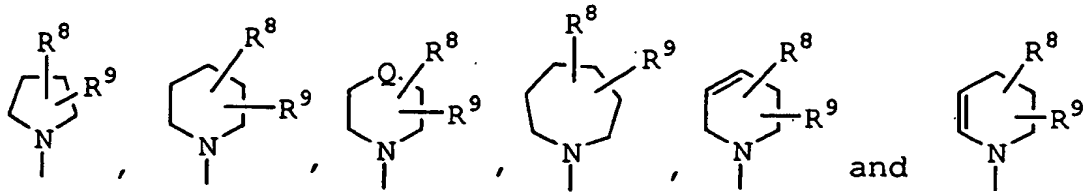
n and m are independently 0 or 1; and

Z is direct bond or bivalent residue derived from piperazine, or a salt thereof.

2. The compound of claim 1 wherein

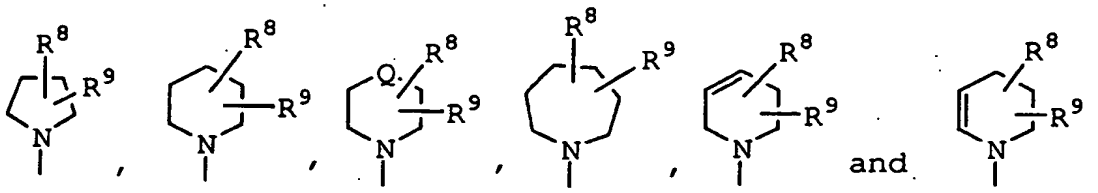
$R^1$ and $R^2$ are each independently lower alkyl, or $R^1$, $R^2$ and nitrogen atom to which they are attached form a

saturated or partially saturated N-containing heterocyclic group selected from



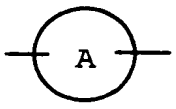
wherein $R^8$ and $R^9$ are each independently hydrogen or lower alkyl, and Q is $-N(R^{10})-$, $-O-$, $-S-$, $-SO-$ or $-SO_2-$ wherein $R^{10}$ is hydrogen or lower alkyl;

$R^3$ is hydrogen, halogen, lower alkyl, lower alkoxy, halo(lower)alkyl or $-NR^5R^6$ (wherein $R^5$ and $R^6$ are each independently lower alkyl, or $R^5$, $R^6$ and nitrogen atom to which they are attached form a saturated or partially saturated N-containing heterocyclic group selected from



wherein $R^8$, $R^9$ and Q are as defined above);

$R^4$ is phenyl, pyridinyl, pyrimidinyl or thiazolyl, each of which is optionally substituted with cyano, amino, lower alkyl or pyrrolyl substituted with one or more lower alkyl; and



is phenylene, pyridinediyl or indolinediyl, or a salt thereof.

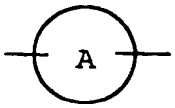
3. The compound of claim 1 wherein

$R^1$ and $R^2$ are each independently lower alkyl;

$R^3$ is hydrogen, halogen, lower alkyl, lower alkoxy or halo(lower)alkyl;

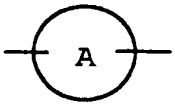
$R^4$ is phenyl, pyridinyl, pyrimidinyl or thiazolyl, each of which is optionally substituted with cyano, amino, lower alkyl or pyrrolyl substituted with one or more lower

alkyl; and



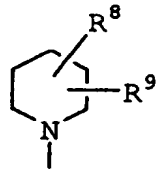

is phenylene,
or a salt thereof.

4. The compound of claim 1 wherein
$R^1$ and $R^2$ are each independently lower alkyl;
$R^3$ is hydrogen, halogen, lower alkyl, lower alkoxy or halo(lower)alkyl;
$R^4$ is phenyl, pyridinyl, pyrimidinyl or thiazolyl, each of which is optionally substituted with cyano, amino, lower alkyl or pyrrolyl substituted with one or more lower alkyl; and

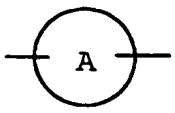



is indolinediyl,
or a salt thereof.

5. The compound of claim 1 wherein
$R^1$, $R^2$ and nitrogen atom to which they are attached form a saturated N-containing heterocyclic group of the formula

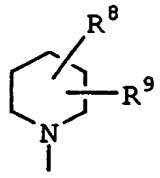



wherein $R^8$ and $R^9$ are each independently hydrogen or lower alkyl;
$R^3$ is hydrogen, halogen, lower alkyl, lower alkoxy or halo(lower)alkyl;
$R^4$ is phenyl, pyridinyl, pyrimidinyl or thiazolyl, each of which is optionally substituted with cyano, amino, lower alkyl or pyrrolyl substituted with one or more lower alkyl; and

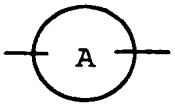



is phenylene,
or a salt thereof.

6. The compound of claim 1 wherein
$R^1$, $R^2$ and nitrogen atom to which they are attached form a saturated N-containing heterocyclic group of the formula




wherein $R^8$ and $R^9$ are each independently hydrogen or lower alkyl;
$R^3$ is hydrogen, halogen, lower alkyl, lower alkoxy or halo(lower)alkyl;
$R^4$ is phenyl, pyridinyl, pyrimidinyl or thiazolyl, each of which is optionally substituted with cyano, amino, lower alkyl or pyrrolyl substituted with one or more lower alkyl; and




is indolinediyl,
or a salt thereof.

7. The compound of claim 1 or a pharmaceutically acceptable salt thereof for use as a medicament.

8. A pharmaceutical composition comprising a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier.

9. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof for preparing a medicament as an apolipoprotein B (Apo B) secretion inhibitor.

10. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof for preparing a medicament for the prophylaxis or treatment of a disease or condition resulting from elevated circulating levels of Apo B.

11. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof for preparing a medicament for the prophylaxis or treatment of hyperlipemia, hyperlipidemia, hyperlipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, atherosclerosis, pancreatitis, non-insulin dependent diabetes mellitus (NIDDM), obesity, coronary heart diseases, myocardial infarction, stroke, restenosis or Syndrome X.

12. A method for inhibiting or decreasing Apo B secretion in a mammal, which comprises administering an Apo B secretion inhibiting or decreasing amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof to the mammal.

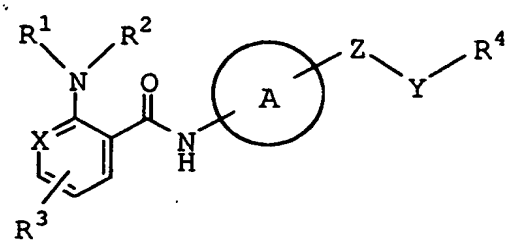
13. A method for preventing or treating a disease or condition resulting from elevated circulating levels of Apo B in a mammal, which comprises administering an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof to the mammal.

14. The method of claim 13 wherein the disease or condition resulting from the elevated circulating levels of Apo B is selected from the group consisting of hyperlipemia, hyperlipidemia, hyperlipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, atherosclerosis, pancreatitis, non-insulin dependent diabetes mellitus (NIDDM), obesity, coronary heart diseases, myocardial infarction, stroke, restenosis and Syndrome X.

DATED this 29th day of October, 2002
**Fujisawa Pharmaceutical C ., Ltd. and**
**DAISO CO., LTD.**
By DAVIES COLLISON CAVE
Patent Attorneys for the Applicant

ABSTRACT

The present invention relates to a compound of the formula (I)



(I)

wherein $R^1$ and $R^2$ are each lower alkyl, or $R^1$, $R^2$ and nitrogen atom to which they are attached form an optionally substituted, saturated or partially saturated N-containing heterocyclic group; $R^3$ is hydrogen, halogen, lower alkyl, lower alkoxy, halo(lower)alkyl or $-NR^5R^6$; $R^4$ is aryl or heteroaryl, each of which is optionally substituted; A is bivalent residue derived from aryl or heteroaryl; X is N or $C(R^3)$; Y is $-(A^1)_n-(A^2)_m-$ wherein $A^1$ is -O-, -NH-, $-N(R^7)-$, -CO- or -NH-CO-, wherein $R^7$ is amino protective group, $A^2$ is lower alkylene, and n and m are independently 0 or 1; and Z is direct bond or bivalent residue derived from piperazine, or a salt thereof. The compound of the present invention and a salt thereof inhibit apolipoprotein B (Apo B) secretion and are useful as a medicament for prophylactic and treatment of diseases or conditions resulting from elevated circulating levels of Apo B.